Supplemental Online Content

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eReferences

This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1. Data Sources and Search strategies

Example of an online strategy run in Web of Science

#1

TS= ("Glucagon-Like Peptide-1Receptor" OR "glucagon like peptide 1 receptor agonist" OR "glp 1 agonist" OR "glp 1 receptor agonist" OR "glucagon like peptide 1 receptor stimulating agent" OR "long acting glp 1 agonist" OR "long acting glp 1 receptor agonist" OR "long acting glp 1 receptor agonist" OR "long acting glucagon like peptide 1 agonist" OR "long acting glucagon like peptide 1 receptor agonist" OR "dulaglutide" OR "liraglutide" OR "exenatide" OR "albiglutide" OR "semaglutide" OR "lixisenatide")

#2

TS=("randomi?ed trial" OR "clinical trial" OR "randomi?ed" OR "random allocation" OR random* OR "controlled trial" OR "randomized controlled trial")

#3

TS= (retraction of publication or retracted publication)

#4

#2 OR #3

#5

#1 AND #4

eMethods 2. Identifications of the outcomes

We identified the gallbladder or biliary diseases based on the classifications in the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. The biliary diseases were captured with the preferred terms (PTs), which include bile duct stone, bile duct obstruction, bile duct stenosis, biliary colic, biliary fistula, biliary cyst, and cholangitis. The lowest level terms (LLTs) that fell into the PTs listed above were also included.

eTable 1. Eligibility criteria of included studies

	Inclusion criteria	Exclusion criteria
Participants	Adults (≥ 18 or 20 years old); with type 2 diabetes, prediabetes, obesity, overweight, nonalcoholic steatohepatitis, and/or metabolic syndrome	Pregnant women; type 1 diabetes; Participants receiving GLP-1RAs treatments before the trials.
Intervention	Any of the six types of GLP-1RAs, including liragkutide, semaglutide, exenatide, dulaglutide, lixisenatide, albiglutide; GLP-1RAs could be in any dose and frequency; GLP-1RAs could be used as monotherapy or add-on treatments to other interventions.	Co-formulation of fixed-dose combinations of GLP-1RAs other anti-diabetic drugs (e.g., IDegLira is a fixed-ratio combination of insulin degludec and liraglutide)
Comparators	Placebo, non-GLP-1RAs medications; non-pharmaceutical treatment (e.g., dietary management, physical exercise)	Comparison of different GLP-1RAs individuals; comparison of different doses of one type of GLP-1RAs (e.g., dulaglutide 3.0mg vs. dulaglutide 1.5mg); comparison of different formulation of one type of GLP-1RAs (subcutaneous semaglutide vs. oral semaglutide); comparison of different frequency of one type of GLP-1RAs (e.g., exenatide BID vs. exenatide QW)
Outcomes	Primary outcome: gallbladder or biliary diseases; Secondary outcomes: the subcategories of gallbladder or biliary diseases.	No primary or secondary outcome data available, either effect estimate for compared groups or number/rate of events in each group.
Study design/Settings	Randomized controlled clinical trials (RCTs)	Reviews or non-RCTs; cross-over study designs; post hoc analyses of the same trial data; uncompleted or withdrawn studies

Note: GLP-1RAs: glucagon-like peptide 1 receptor agonists; RCTs, randomized controlled clinical trials.

eTable 2. Baseline characteristics of studies and participants included

Trials	No. of participant s	Treatment duration	Population	Age (year)	No. (%) of female	BMI (kg/m²)	Weight (kg)	HbA1c (%)	Interventions	Controls
Liraglutide										
LEAD-1 (2009)	1041	26 weeks	T2DM with OAD; BMI ≤ 45 kg/m²	55.9	526 (50.5%)	29.9	81.6	8.4%	Liraglutide 0.6 mg; liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Placebo; rosiglitazone
LEAD-4 (2009)	510	26 weeks	T2DM with OAD; BMI ≤ 45 kg/m ²	55.0	289(56.7%)	33.5	-	8.5%	liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Placebo
Seino et. al. (2010)	400	24 weeks	T2DM; BMI < 35 kg/m ²	58.3	132 (33.0%)	24.5	65.0	8.9%	Liraglutide 0.9 mg, daily	Glibenclamide
LEAD-3 Mono (2011)	745	104 weeks	T2DM with oral monotherapy; BMI≤ 45 kg/m²	53.0	375 (50.3%)	33.1	92.9	8.4%	Liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Glimepiride
1860-LIRA- DPP-4 (2011)	658	52 weeks	T2DM with metformin; BMI < 45 kg/m ²	55.9	316 (48.0%)	32.8	93.8	8.4%	Liraglutide 1.2 mg; liraglutide 1.8 mg; daily	Sitagliptin
Astrup et. al. (2012)	466	104 weeks	BMI 30-40 kg/m ² ; without T1DM or T2DM	45.9	355 (76.2%)	34.7	97.2	-	Liraglutide 1.2 mg; liraglutide 1.8 mg; liraglutide 2.4 mg; liraglutide 3.0 mg; daily	Orlistat
SCALE Maintenance (2013)	422	56 weeks	BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² if the patient had dyslipidemia or hypertension	46.2	344 (81.5%)	36.0	100.4	5.6%	Liraglutide 3.0 mg, daily	Placebo
SCALE Sleep Apnea (2013)	355	32 weeks	OSA; BMI > 30 kg/m ²	48.5	101 (28.1%)	38.1	-	-	Liraglutide 3.0 mg, daily	Placebo
SCALE Obesity and Prediabetes (2015) ^a	1444	56 weeks	BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² if the patient had dyslipidemia or hypertension; without prediabetes	41.5	1194 (82.7%)	37.4	103.8	5.3%	Liraglutide 3.0 mg, daily	Placebo
SCALE Diabetes	844	58 weeks	T2DM; overweight or obese (BMI > 27 kg/m²)	54.9	421 (49.9%)	37.2	106.0	7.9%	Liraglutide 1.8 mg; liraglutide 3.0 mg; daily	Placebo

(2015)										
EAGLE study (2015)	965	24 weeks	T2DM; BMI > 25 kg/m ²	57.3	431 (44.7%)	31.9	90.5	9.1%	Liraglutide 1.8 mg, daily	Insulin glargine
LEADER (2016)	9360	3.8 years	T2DM with high risks of CVD	64.3	3337 (35.6%)	32.5	91.9	8.7%	Liraglutide 1.8 mg, daily	Placebo
LIRA-RENAL (2016)	277	26 weeks	T2DM with moderate renal impairments; BMI 25-45 kg/m ²	67.2	137 (49.5%)	33.5	94.6	8.1%	Liraglutide 1.8 mg, daily	Placebo
SCALE Obesity and Prediabetes (2017) ^a	2248	3 years	BMI ≥ 30 kg/m² or BMI ≥ 27 kg/m² if the patient had dyslipidemia or hypertension; with prediabetes	47.4	1714 (76.5%)	38.9	107.7	5.8%	Liraglutide 3.0 mg, daily	Placebo
Larsen et. al. (2017)	100	16 weeks	Schizophrenia spectrum disorder; prediabetes; BMI ≥ 27 kg/m²	42.5	37 (38.1%)	33.8	102.8	5.6%	Liraglutide 1.8mg, daily	Placebo
LIPT study (2017)	72	26 weeks	Woman with PCOS and/or presence of IR; BMI>25 kg/m ²	28.8	72 (100%)	33.3	92.7	5.3%	Liraglutide 1.8 mg, daily	placebo
SCALE-IBT (2020)	282	56 weeks	BMI ≥ 30 kg/m ²	47.2	235 (83.3%)	39.0	107.6	5.5%	Liraglutide 3.0 mg + IBT, daily	Placebo + IBT
SCALE Insulin (2020)	392	56 weeks	T2DM; BMI > 27 kg/m ²	56.7	207 (52.3%)	35.6	99.7	7.9%	Liraglutide 3.0 mg + IBT + insulin, daily	Placebo + IBT + insulin
LIRA- ADD2SGLT2i (2020)	302	26 weeks	T2DM with SGLT-2i; BMI > 20 kg/m ²	55.2	120 (40%)	32.2	91.1	8.0%	Liraglutide 1.8 mg, daily	Placebo
Lundgren et.al. (2021)	195	1.0 year	BMI 32-43 kg/m ²	43.0	25 (63%)	32.6	96.7	5.3%	Liraglutide 3.0 mg, Liraglutide 3.0 mg + exercise; daily	Placebo; exercise
Subcutaneous	semaglutide									
SUSTAIN-1 (2017)	387	30 weeks	T2DM treated with diet and exercise alone	53.7	177 (46%)	32.9	91.9	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
SUSTAIN-2	1225	56 weeks	T2DM with OAD	55.1	605 (49.4%)	32.5	89.5	8.1%	Semaglutide 0.5mg;	Sitagliptin

(2017)									semaglutide 1.0mg; weekly	
SUSTAIN-4 (2017)	1082	30 weeks	T2DM with metformin; insulin-naïve patients	56.5	508 (47%)	33.0	93.5	8.2%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Insulin glargine
SUSTAIN-6 (2017)	3297	104 weeks	T2DM with high risks of CVD	64.6	1295(39.3%)	32.8	92.1	8.7%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
SUSTAIN-5 (2018)	396	30 weeks	T2DM with basal insulin and/or metformin therapy	58.8	174 (43.9%)	32.2	91.7	8.4%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Placebo
Seino et. al. (2017)	308	30 weeks	T2DM with or without OAD monotherapy	58.3	73 (23.7%)	25.4	69.3	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Sitagliptin
M O'Neil et. al. (2018)	854	52 weeks	BMI ≥ 30 kg/mg² without diabetes	47.0	545 (64.3%)	39.3	111.5	5.5%	Semaglutide 0.05 mg, 0.1mg, 0.2mg, 0.3mg, 0.4mg; daily	Placebo
Kaku et. al. (2018)	600	56 weeks	T2DM with or without OAD monotherapy	58.5	171(0.285)	26.4	71.5	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Additional OAD
SUSTAIN-8 (2019)	786	52 weeks	T2DM with metformin treatments	56.6	364 (46%)	32.3	90.2	8.3%	Semaglutide 1.0mg; weekly	Canagliflozin
SUSTAIN- China (2021)	867	30 weeks	T2DM with metformin monotherapy	53.0	367 (42.6%)	27.8	76.4	8.1%	Semaglutide 0.5mg; semaglutide 1.0mg; weekly	Sitagliptin
STEP-1 (2021)	1961	68 weeks	BMI ≥ 30 kg/mg ² or BMI ≥ 27 kg/mg ² with one or more coexisting conditions	46.5	1453 (74.1%)	37.9	105.3	5.7%	Semaglutide 2.4 mg; weekly	Placebo
STEP-2 (2021)	1210	68 weeks	T2DM; BMI ≥ 27 kg/mg ² ; failed with dietary effort to lose weight	55.0	616 (50.9%)	35.7	99.8	8.1%	Semaglutide 1.0 mg; semaglutide 2.4 mg; weekly	Placebo
STEP-3 (2021)	611	68 weeks	BMI ≥ 30 kg/mg² or BMI ≥ 27 kg/mg² with one or more coexisting	46.0	495 (81.0%)	38.0	105.3	5.7%	Semaglutide 2.4 mg; weekly	Placebo

			conditions							
Newsome et. al. (2021)	319	72 weeks	NASH or NAFLD; BMI ≥ 25 kg/mg ² ; with or without T2DM	55.0	194 (60.8%)	35.7	98.4	7.3%	Semaglutide 0.1 mg; Semaglutide 0.2 mg; Semaglutide 0.4 mg; daily	Placebo
Oral semaglutide										
Davies et. al. (2017)	421	26 weeks	T2DM with management only by diet and exercise or metformin; BMI 25-40 kg/m ²	57.2	214 (38.1%)	31.9	92.8	7.9%	Oral semaglutide 5 mg, 10mg, 20 mg, 40mg; daily	Placebo
PIONEER-1 (2019)	703	26 weeks	T2DM with management only by diet and exercise	55.0	346 (49.2%)	31.8	88.1	8.0%	Oral semaglutide 14 mg; daily	Placebo
PIONEER-2 (2019)	819	52 weeks	T2DM with metformin	58.0	406 (49.5%)	32.8	91.6	8.1%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Empagliflozin
PIONEER-3 (2019)	1861	78 weeks	T2DM with metformin treatments; with or without sulfonylurea	58.0	879 (47.2%)	32.4	91.3	8.3%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Sitagliptin
PIONEER-4 (2019)	714	52 weeks	T2DM with metformin treatments	56.0	341 (48%)	33.0	94.0	8.0%	Oral semaglutide 14 mg; liraglutide 1.8mg; daily	Placebo
PIONEER-6 (2019)	3183	82 weeks	T2DM with high risks of CVD or CKD	66.0	1007 (31.6%)	32.3	90.9	8.2%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Placebo
PIONEER-7 (2019)	503	52 weeks	T2DM with other OAD	57.4	219 (43.5%)	31.5	88.6	8.3%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Sitagliptin
PIONEER-8 (2019)	730	52weeks	T2DM with insulin therapy	61.0	336 (46%)	31.0	85.9	8.2%	Oral semaglutide 3mg, 7 mg, 14 mg; daily	Placebo
Dulaglutide										
AWARD-1 (2014)	700	26 weeks	T2DM with OAD monotherapy; BMI 23-45 kg/m ²	56.0	406 (58.0%)	33.0	96	8.1%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Placebo
Ferdinand et. al. (2014)	755	26 weeks	T2DM with OAD treatments; BMI ≥ 23 kg/m²	56.5	363 (48.1%)	33.0	-	7.9%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Placebo
AWARD-2	807	52 weeks	T2DM with OAD	56.6	393 (48.7%)	31.5	86.3	8.1%	Dulaglutide 0.75mg;	Insulin glargine

(2015)			treatments; BMI 23- 45kg/m ²						dulaglutide 1.5mg; weekly	
AWARD-3 (2015)	807	26 weeks	T2DM with one OAD monotherapy or diet and exercise alone	56.7	454 (56.3%)	33.3	92.3	7.6%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Metformin
AWARD-4 (2015)	884	52 weeks	T2DM; BMI 23-45 kg/m ²	59.4	411 (46.5%)	32.5	91.2	8.4%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
AWARD-5 (2015)	1098	104 weeks	T2DM with other OAD; BMI 25-40 kg/m ²	54.0	577 (52.5%)	31.0	86.5	8.1%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Sitagliptin; placebo
Araki et. al. (2015)	361	26 weeks	T2DM with sulphonylureas and/or metformin; BMI 18.5-35 kg/m ²	56.8	107 (29.0%)	26.0	71.0	8.0%	Dulaglutide 0.75mg; weekly	Insulin glargine
AWARD-7 (2018)	576	52 weeks	T2DM with moderate-to- severe renal impairments; with insulin treatments	64.5	275 (47.7%)	32.5	89.1	8.6%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
AWARD-CHN1 (2018)	735	26 weeks	T2DM with OAD-naïve or OAD monotherapy; BMI 19-35 kg/m ² ;	52.8	329 (45.7%)	26.2	-	8.0%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Glimepiride
AWARD-CHN2 (2018)	768	52weeks	T2DM with metformin and/or sulphonylurea; BMI 19-35 kg/m ²	55.0	338 (44.8%)	26.8	73.9	8.4%	Dulaglutide 0.75mg; dulaglutide 1.5mg; weekly	Insulin glargine
REWIND (2019)	9892	7 years	T2DM with high risks of CVD or CKD; BMI≥23 kg/m ²	66.2	4589 (46.4%)	32.3	-	7.3%	Dulaglutide 1.5 mg; weekly	Placebo
Exenatide										
Heine et. al. (2005)	549	26 weeks	T2DM with inadequate glycemic control; BMI 25- 45 kg/m²	58.9	243 (44.2%)	31.4	87.9	8.2%	Exenatide 10 µg, twice daily	Insulin glargine
DURATION-2 (2010)	491	26 weeks	T2DM with metformin treatments; BMI 25-45 kg/m ²	52.3	237 (48.3%)	32.0	88.0	8.6%	Exenatide 2 mg, weekly	Pioglitazone; sitagliptin

Inagaki et. al. (2012)	427	52 weeks	T2DM with other OAD; BMI 18-35 kg/m²	56.8	137 (32.1%)	26.2	70.5	8.5%	Exenatide 2 mg, weekly	Insulin glargine
EUREXA (2012)	1019	4.5 years	T2DM with metformin; BMI 25-40 kg/m ²	56.0	457 (46.4%)	32.	91.9	7.5%	Exenatide 10 µg, twice daily	Glimepiride
DURATION-3 (2014)	447	104 weeks	T2DM with metformin; BMI 25-45 kg/m ²	58.0	120 (52%)	32.5	91.2	8.3%	Exenatide 2 mg, weekly	Insulin glargine
Diamant et. al. (2014)	627	30 weeks	T2DM with other OAD; BMI ≥ 25 kg/m ²	59.5	134 (51.0%)	32.5	90.3	8.3%	Exenatide 10 µg + insulin glargine; twice daily	Insulin lispro + insulin glargine
Jaiswal et. al. (2015)	46	78 weeks	T2DM with mild-to- moderate DPN; with other OAD	53.0	20 (43.5%)	36.5	108.	8.3%	Exenatide 10 µg, twice daily	Insulin glargine
EXCEL (2017)	14737	7.5 years	T2DM with previous CVD	62.0	5603(38.0%)	31.8	-	8.0%	Exenatide 2 mg, weekly	Placebo
DURATION-8 (2020)	694	104 weeks	T2DM with inadequate glycemic control	54.3	357 (52.1%)	32.7	90.9	9.3%	Exenatide 2mg; exenatide 2mg + dapagliflozin; weekly	Dapagliflozin
Lixisenatide										
GETGOAL- Duo1 (2013)	446	24 weeks	T2DM with metformin and/or other OAD; BMI > 20 kg/m ²	56.0	224 (50%)	31.8	87.	7.6%	Lixisenatide 20 µg + insulin glargine + metformin, daily	Placebo + insulin glargine + metformin
GETGOAL-M (2013)	680	24 weeks	T2DM with metformin treatments	54.8	387 (56.9%)	32.9	90.1	8.1%	Lixisenatide 20 µg daily	Placebo
GETGOAL-P (2013)	484	24 weeks	T2DM with pioglitazone treatments	55.6	237 (60.0%)	34.0	94.8	8.1%	Lixisenatide 20 µg daily	Placebo
GETGOAL-F1 (2013)	483	24 weeks	T2DM with metformin monotherapy	56.1	266 (55.2%)	32.5	88.7	8.0%	Lixisenatide 20 µg daily	Placebo
GETGOAL-S (2014)	859	24 weeks	T2DM with sulphonylureas treatments	57.4	425 (49.5%)	30.3	83.6	8.2%	Lixisenatide 20 µg daily	Placebo
ELIXA (2015)	6063	225 weeks	T2DM with acute coronary events	59.8	1861(30.7%)	30.1	84.8	7.7%	Lixisenatide 20 µg daily	Placebo
Albiglutide										

HARMONEY-1 (2014)	301	52 weeks	T2DM with pioglitazone; BMI 20-45 kg/m² with or Without metformin	55.0	121 (40.2%)	34.1	98.9	8.1%	Albiglutide 30 mg + Pioglitazone; weekly	Placebo + pioglitazone
HARMONEY-3 (2014)	1012	104 weeks	T2DM with metformin; BMI 20-45 kg/m ²	54.8	530 (52.4%)	32.6	90.8	8.1%	Albiglutide 30-50 mg; weekly	Placebo; sitagliptin; glimepiride
HARMONEY-4 (2014)	745	52 weeks	T2DM with metformin; BMI 20-45 kg/m ²	55.5	327 (43.9%)	33.1	94.9	8.3%	Albiglutide 30 mg + metformin; weekly	Insulin glargine+ metformin
Rosenstock et. al. (2014)	566	52 weeks	T2DM with insulin; BMI 20-45 kg/m ²	55.5	298 (52.6%)	-	92.1	8.4%	Albiglutide 30 mg+ insulin glargine; weekly	Lispro insulin + insulin glargine
Leiter et. al. (2014)	495	52 weeks	T2DM with renal impairments; BMI 20-45 kg/m ²	63.3	229 (46.3%)	30.4	80.0	8.2%	Albiglutide 30 mg, weekly	Sitagliptin
HARMONEY-5 (2015)	663	52 weeks	T2DM with metformin and sulphonylureas; BMI 20-45 kg/m ²	55.2	310 (46.8%)	32.2	90.8	8.2%	Albiglutide 30 mg, weekly	Placebo; pioglitazone
Harmony outcome (2018)	9432	1.5years	T2DM with established CVD	64.1	2894 (30.3%)	32.3	-	8.7%	Albiglutide 30-50 mg, weekly	Placebo
Rosenstock et. al. (2020)	813	26 weeks	T2DM with basal plus prandial insulin	58.0	442 (54.4%)	32.3	88.8	7.7%	Albiglutide 50 mg+ insulin glargine; weekly	Insulin lispro + insulin glargine

Notes: BMI, body mass index; T2DM, type 2 diabetes mellitus; SGLT-2i, sodium-glucose cotransporter-2 inhibitors; T1DM, type 1 diabetes mellitus; CVD, cardiovascular diseases; CKD, chronic kidney disease; OAD, oral anti-diabetic drugs; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; PCOS: polycystic ovary syndrome.

^a The SCALE Obesity and Prediabetes trial was divided into two groups (participants with or without prediabetes) because they had different follow-up periods.

eTable 3. Assessments of risks of bias of eligible studies according to Revised Cochrane risk-of-bias tool for randomized trials

Trials	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	No. of participants
LEAD-1(2009) ¹	some concerns	low	some concerns	low	low	1041
LEAD-4 (2009) ²	low	low	low	low	some concerns	510
Seino et. al. (2010) ³	low	low	low	low	some concerns	400
LEAD-3 Mon (2011) ⁴	low	low	low	low	some concerns	745
1860-LIRA-DPP-4 (2011) ⁵	low	some concerns	some concerns	low	some concerns	658
Astrup et. al. (2012) ⁶	low	some concerns	some concerns	low	some concerns	466
SCALE Maintenance (2013) ⁷	low	low	low	low	some concerns	422
SCALE Sleep Apnea (2013) ⁸	low	low	some concerns	low	low	355
SCALE Obesity and Prediabetes (2015) ⁹	low	low	some concerns	low	some concerns	1444
SCALE Diabetes (2015) ¹⁰	low	low	low	low	low	844
EAGLE study (2015) ¹¹	low	some concerns	low	low	low	965
LEADER (2016) ¹²	low	low	low	low	low	9360
LIRA-RENAL (2016) ¹³	low	low	low	low	some concerns	277
SCALE Obesity and Prediabetes (2017) ¹⁴	low	low	low	low	low	2248
Larsen et. al. (2017) ¹⁵	low	low	low	low	low	100
LIPT (2017) ¹⁶	low	low	low	low	low	72
SCALE-IBT (2020) ¹⁷	low	low	low	low	low	282
SCALE Insulin (2020) ¹⁸	low	low	low	low	low	392
LIRA-ADD2SGLT2i (2020) ¹⁹	low	low	low	low	low	302
Lundgren et.al. (2021) ²⁰	low	low	low	low	low	195
SUSTAIN-1(2017) ²¹	low	low	low	low	low	387
SUSTAIN-2(2017) ²²	low	low	low	low	low	1225
SUSTAIN-4(2017) ²³	low	low	low	low	low	1082
SUSTAIN-6(2017) ²⁴	low	low	low	low	low	3297
Seino et. al. (2017) ²⁵	low	some concerns	low	low	some concerns	308
SUSTAIN-5 (2018) ²⁶	low	low	low	low	low	396
M O'Neil et. al. (2018) ²⁷	some concerns	low	some concerns	low	low	854
Kaku et. al. (2018) ²⁸	low	some concerns	low	low	low	600
SUSTAIN-8 (2019) ²⁹	low	low	low	low	some concerns	786
SUSTAIN China (2021) ³⁰	low	low	low	low	some concerns	867
STEP-1(2021) ³¹	low	low	low	low	low	1961
STEP-2(2021) ³²	low	low	low	low	low	1207

STEP-3(2021)33	low	low	low	low	low	611
Newsome et. al. (2021) ³⁴	low	low	low	low	low	319
Davies et. al. (2017) ³⁵	low	some concerns	low	low	Some concerns	421
PIONEER-1(2019) ³⁶	low	low	low	low	some concerns	703
PIONEER-2(2019) ³⁷	low	some concerns	low	low	some concerns	819
PIONEER-3 (2019) ³⁸	low	low	low	Some concerns	some concerns	1861
PIONEER-4 (2019) ³⁹	low	low	low	low	some concerns	714
PIONEER-6 (2019) ⁴⁰	low	low	low	low	low	3183
PIONEER-7 (2019) ⁴¹	low	low	low	low	some concerns	503
PIONEER-8 (2019) ⁴²	low	low	low	low	some concerns	730
AWARD-1 (2014) ⁴³	some concerns	low	low	low	some concerns	700
Ferdinand et. al. (2014) ⁴⁴	low	low	low	low	some concerns	755
AWARD-2 (2015) ⁴⁵	low	some concerns	low	low	some concerns	807
AWARD-3 (2015) ⁴⁶	low	low	low	low	some concerns	807
AWARD-4 (2015) ⁴⁷	low	low	low	low	some concerns	884
AWARD-5 (2015) ⁴⁸	low	low	some concerns	low	some concerns	1098
Araki et. al. (2015) ⁴⁹	low	some concerns	low	low	low	361
AWARD-7 (2018) ⁵⁰	low	low	low	low	some concerns	576
AWARD-CHN1(2018)51	low	low	low	low	low	735
AWARD-CHN2 (2018) ⁵²	low	some concerns	low	low	some concerns	768
REWIND (2019) ⁵³	low	low	low	low	low	9892
Heine et. al. (2005) ⁵⁴	low	some concerns	low	low	some concerns	549
DURATION-2 (2010) ⁵⁵	low	low	low	low	some concerns	491
EUREXA (2012) ⁵⁶	low	low	some concerns	low	some concerns	1019
Inagaki et. al. (2012) ⁵⁷	low	some concerns	low	low	low	427
DURATION-3 (2014) ⁵⁸	low	low	some concerns	low	Some concerns	447
Diamant et. al. (2014) ⁵⁹	low	low	some concerns	low	low	627
Jaiswal et. al. (2015) ⁶⁰	low	some concerns	low	low	low	46
DURATION-8 (2016) ⁶¹	some concerns	low	some concerns	low	some concerns	694
EXCEL (2017) ⁶²	low	low	low	low	low	14737
GETGOAL-Duo1 (2013) ⁶³	low	low	low	low	some concerns	446

				1		
GETGOAL -M (2013) ⁶⁴	low	some concerns	low	low	some concerns	680
GETGOAL-S (2013) ⁶⁵	low	low	low	low	some concerns	859
GETGOAL-P (2013) ⁶⁶	low	some concerns	low	low	some concerns	484
GETGOAL-F1 (2013) ⁶⁷	low	low	low	low	some concerns	483
ELIXA (2015) ⁶⁸	low	low	low	low	low	6063
HARMONEY-1(2014) ⁶⁹	low	low	low	low	some concerns	301
HARMONEY-3 (2014) ⁷⁰	low	low	some concerns	low	some concerns	1012
HARMONEY-4 (2014) ⁷¹	low	low	low	low	some concerns	745
Rosenstock et. al. (2014) ⁷²	low	some concerns	low	low	some concerns	566
Leiter et. al. (2014) ⁷³	low	some concerns	some concerns	low	some concerns	495
HARMONEY-5 (2015) ⁷⁴	low	low	low	low	Some concerns	663
Harmony outcome (2018) ⁷⁵	low	low	low	low	low	9432
Rosenstock et. al. (2020) ⁷⁶	low	low	low	low	some concerns	813

Notes: Domain 1: Risk of bias arising from the randomization process. Domain 2: Risk of bias due to deviations from the intended interventions. Domain 3: Risk of bias due to missing outcome data. Domain 4: Risk of bias in measurement of the outcome. Domain 5: Risk of bias in selection of the reported results.

eTable 4. GRADE summary of findings for each outcome in the meta-analysis

Outcomes	No. of	Study ev	vent rates	Relative	Relative Anticipated absolute effect a		Risk of	Inconsi	Indirect	Impreci	Publica	Certainty
	patients	Experiments	Controls	effects	Risk with	Risk with	bias	stency	ness	sion	tion	of
	(studies)			(95% CI)	controls	GLP-1RAs					bias	evidence
Gallbladder or	103,371	1.58%	1.19%	RR 1.37	70 per 10,000	96 per 10,000	Not	Not	Not	Not	Not	High
biliary diseases	(76 b)	(916/57,856)	(544/45,515)	(1.23, 1.52)		(86 to 107)	serious	serious	serious	serious	serious	$\oplus \oplus \oplus \oplus$
cholelithiasis	95,886	0.85%	0.68%	RR 1.27	46 per 10,000	58 per 10,000	Not	Not	Not	Not	Not	High
	(61 b)	(454/53,674)	(287/42,212)	(1.10, 1.47)		(51 to 67)	serious	serious	serious	serious	serious	$\oplus \oplus \oplus \oplus$
cholecystitis	90,137	0.61%	0.46%	RR 1.36	27 per 10,000	37 per 10,000	Not	Not	Not	Not	Not	High
	(53 b)	(302/49,491)	(187/40,574)	(1.14, 1.62)		(31 to 41)	serious	serious	serious	serious	serious	$\oplus \oplus \oplus \oplus$
Biliary	68,966	0.21%	0.13%	RR 1.55	9 per 10,000	14 per 10,000	Not	Not	Not	Not	Not	Moderate
diseases	(21 b)	(77/36,225)	(41/32,741)	(1.08, 2.22)		(10 to 20)	serious	serious	serious	serious	serious	⊕⊕⊕О°

Notes: GRADE, grading of recommendations assessment, development, and evaluation. GLP-1RAs, glucagon-like peptide 1 receptor agonists; T2DM, type 2 diabetes mellitus; RR, relative risk; CI, confidence intervals.

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

^a The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

b There were a total of 76 trials including 77 sets of data for gallbladder or biliary diseases, 61 trials including 62 sets of data for cholelithiasis, 53 trials for cholecystitis, and 21 trials for biliary diseases.

^c Concerns about selective reporting.

eTable 5. Effects of factors on the risks of gallbladder or biliary diseases with GLP-1RAs in trials with diabetes treatment

Risk factors	No. of	No. of	Relative risks	Hetero	geneity	P-value for
	patients	trials	(95%CI)	l ²	P-value	interaction ^a
Dose of treatments b						0.08
High dose ^c	50,922	37	1.41 (1.21, 1.64)	0%	0.99	
Low dose d	15,913	29	1.04 (0.77, 1.42)	0%	0.62	
Duration of treatmen	its					0.07
≤ 26 weeks	13,229	22	0.78 (0.46, 1.33)	0%	0.96	
> 26 weeks	78,817	39	1.29 (1.15, 1.45)	0%	0.77	
Baseline BMI e						0.14
High	73,830	42	1.23 (1.10, 1.39)	0%	0.80	
Low	17,203	17	1.69 (1.13, 2.53)	0%	0.90	
Control types						0.20
Placebo	68,506	29	1.30 (1.15, 1.47)	0%	0.92	
Active comparators	24,967	35	1.02 (0.73, 1.44)	0%	0.92	
Types of trials	•					0.16
CVOT	55,964	7	1.31 (1.16, 1.48)	22%	0.26	
Non-CVOT	35,635	53	1.05 (0.79, 1.40)	0%	0.98	

Note: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidential intervals; T2DM, type 2 diabetes mellitus; CVOT, cardiovascular outcomes trials; BMI, body mass index.

^a P-value for interaction is used to test groups difference.

^b One trial might have two or more different dose of GLP-1RAs treatments. Among the studies included, only studies with liraglutide, subcutaneous semaglutide, oral semaglutide dulaglutide, and albiglutide had different dose of treatments. Lixisenatide and exenatide with single dose in eligible studies were not included to access the dosage-dependent effects.

^c In trials with GLP-1RAs treatment for diabetes, the high dose groups included liraglutide ≥ 1.8 mg once-daily, subcutaneous semaglutide ≥ 1.0 mg once-weekly, oral semaglutide ≥ 7 mg once-daily, dulaglutide ≥ 1.5 mg once-weekly, and albiglutide ≥ 50 mg once-weekly.

^d In trials with GLP-1RAs treatment for diabetes, low dose of GLP-1RAs included liraglutide 0.6-1.2 mg (< 1.8 mg) daily, subcutaneous semaglutide 0.5 mg (< 1.0 mg) once-weekly, oral semglutide 3.0 mg (< 7.0 mg) once-daily, dulaglutide 0.75 mg (< 1.5 mg) once-weekly, and albiglutide 30 mg (< 50 mg) once-weekly.

 $^{^{\}rm e}$ The cut-off point of the baseline BMI was 31.6 kg/m $^{\rm 2}$ which was the mean of baseline BMI in trials using GLP-1RAs for diabetes.

eTable 6. Effects of factors on the risks of gallbladder or biliary diseases with GLP-1RAs in trials with treatment for weight loss

Risk factors	No. of	No. of	Relative risks	Heter	ogeneity	P-value for	
	patients	trials	(95%CI)	l ²	P-value	interaction ^a	
Baseline BMI b						0.56	
High	8,599	8	2.37 (1.66, 3.39)	0%	0.65		
Low	2,682	5	1.79 (0.76, 4.24)	0%	0.79		
Control types						0.59	
Placebo	11,284	13	2.33 (1.67, 3.24)	0%	0.86		
Active comparators	466	1	1.28 (0.15, 10.83)	-	-		

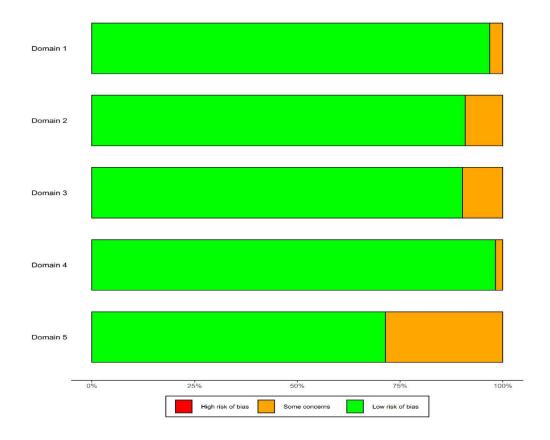
Note: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidential intervals; BMI, body mass index.

^a P-value for interaction is used to test groups difference.

^b The cut-off point of the baseline BMI was 36.7 kg/m² which was the mean of baseline BMI in trials using GLP-1RAs for weight loss.

eFigure 1. Summary of risks of bias of all included studies

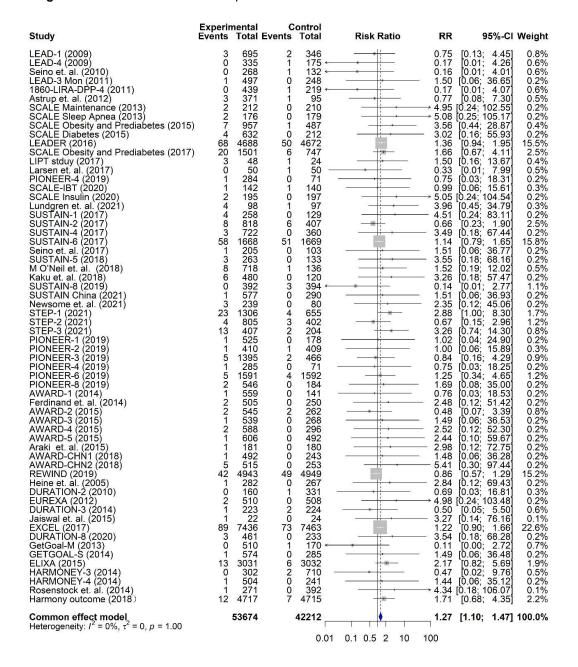
Notes: Domain 1: Risk of bias arising from randomization process Domain 2: Risk of bias due to deviations from intended interventions Domain 3: Risk of bias due to missing outcome data. Domain 4: Risk of bias in outcome measurements. Domain 5: Risk of bias in the selection of reported results.



eFigure 2. Risks of cholelithiasis, cholecystitis, and biliary diseases in patients with GLP-1RAs treatments compared with controls

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; Cl, confidence interval.

eFigure 2A. Risks of cholelithiasis in patients with GLP-1RAs



eFigure 2B. Risks of cholecystitis in patients with GLP-1RAs

Study	Experimental Events Total	Control Events Total	Risk Ratio	RR	95%-CI Weight
LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) SCALE Sleep Apnea (2013) SCALE Obesity and Prediabetes (2015) EAGLE study (2015) LEADER (2016) LIRA-RENAL (2016) SCALE Obesity and Prediabetes (2017) PIONEER-4 (2019) SCALE-IBT (2020) LIRA-ADD2SGLT2i (2020) SUSTAIN-2 (2017) SUSTAIN-6 (2017) SUSTAIN-1 (2017) SUSTAIN-8 (2017) SUSTAIN-9 (2017) SUSTAIN-9 (2017) SUSTAIN-9 (2017) SUSTAIN-9 (2017) SUSTAIN-9 (2017) SUSTAIN-9 (2019) SUSTAIN-9 (2019) SUSTAIN-9 (2019) SUSTAIN-9 (2019) PIONEER-1 (2019) PIONEER-1 (2019) PIONEER-2 (2019) PIONEER-2 (2019) PIONEER-3 (2019) PIONEER-3 (2015) AWARD-7 (2018) AWARD-6 (2015) AWARD-6 (2015) AWARD-6 (2019) SUSTAIN-9 (2018) REWIND (2019) DURATION-2 (2010) EUREXA (2012) Inagaki et. al. 2012 Diamant et. al. (2014) DURATION-3 (2014) EXCEL (2017) DURATION-8 (2020) GETGOAL-P (2013) GETGOAL-P (2013) GETGOAL-P (2013) GETGOAL-P (2013) GETGOAL-P (2013) GETGOAL-P (2014) HARMONEY-1 (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) HARMONEY-4 (2018) Rosenstock et. al. (2020) Common effect model	1 632 1 481 36 4688 1 140	0 248 1 219 ← 179 ← 179 ← 179 ← 179 ← 179 ← 1747		0.17 \(\) (0.34 \\ \) (0.34 \\ \) (0.34 \\ \) (0.34 \\ \) (0.35 \\ \) (0.35 \\ \) (0.36 \\ \) (0.36 \\ \) (0.37 \\ \) (0.37 \\ \) (0.38 \\ \) (0.38 \\ \) (0.39 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.30 \\ \) (0.33 \\ \) (0.33 \\ \) (0.33 \\ \) (0.33 \\ \) (0.33 \\ \) (0.34 \\ \) (0.35 \\ \) (0.35 \\ \) (0.36 \\ \) (0.37 \\ \) (0.37 \\ \) (0.37 \\ \) (0.37 \\ \) (0.34 \\ \) (0.36 \\ \) (0.37 \\ \) (0.34 \\ \) (0.34 \\ \) (0.34 \\ \) (0.34 \\ \) (0.34 \\ \) (0.36 \\ \) (0.37 \\ \) (0.34 \\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\	.06; 36.65] 0.3% .001; 4.07] 0.9% .06; 26.55] 0.4% .001; 8.27] 0.7% .37; 25.29] 0.6% .04; 24.65] 0.4% .12; 73.92] 0.2% .100; 2.92] 9.9% .12; 71.45] 0.2% .99; 56.41] 0.4% .03; 18.31] 0.4% .03; 18.31] 0.4% .06; 36.65] 0.3% .06; 36.65] 0.3% .06; 36.65] 0.3% .06; 36.65] 0.3% .07; 25.41] 0.4% .001; 8.20] 0.7% .18; 67.94] 0.3% .31; 99.35] 0.3% .10; 14.06] 0.4% .03; 14.87] 0.4% .04; 24.90] 0.4% .04; 24.90] 0.4% .06; 36.28] 0.3% .12; 45.06] 0.4% .06; 36.28] 0.3% .12; 45.06] 0.4% .07; 25.41] 0.4% .08; 16.81] 0.5% .09; 16.6] 34.2% .00; 18.81] 0.5% .00; 18.81] 0.5% .00; 18.81] 0.7% .01; 8.07] 0.7% .01; 8.07] 0.7% .02; 5.30] 0.7% .03; 16.81] 0.5% .06; 36.28] 0.3% .24; 81.89] 0.3% .12; 2.60] 15.9% .00; 1.66] 34.2% .00; 1.32] 0.3% .01; 8.07] 0.7% .06; 36.56] 0.3% .07; 3.56] 1.2% .07; 3.56] 1.2% .08; 16.81] 0.5% .09; 1.66] 34.2% .09; 1.66] 34.2% .00; 1.32] 0.3% .00; 1.32] 0.3% .00; 1.32] 0.3% .00; 1.32] 0.3% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2% .00; 1.32] 0.2%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 0.99$		0.01	0.1 0.5 2 10	100	± 10.8

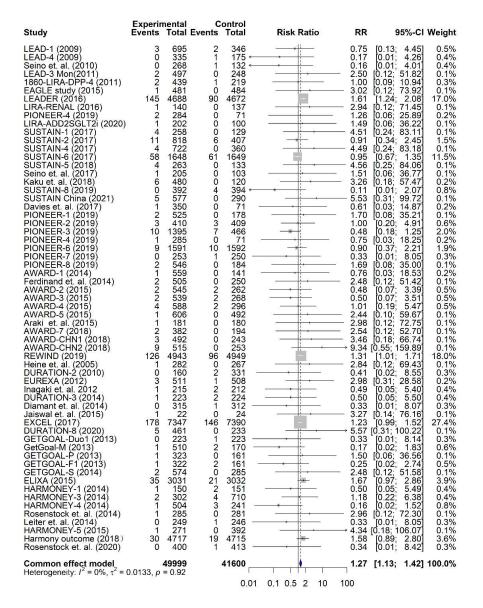
eFigure 2C. Risks of biliary diseases in patients with GLP-1RAs

Study	Experin Events		C Events	ontrol Total		Risk	Ratio	RR	95%-CI	Weight
1860-LIRA-DPP-4 (2011) SCALE Obesity and Prediabetes (2015) SCALE Diabetes (2015) LEADER (2016) SCALE Obesity and Prediabetes (2017) SUSTAIN-6 (2017) SUSTAIN China (2021) STEP-3 (2021) Newsome et. al. (2021) PIONEER-3 (2019) PIONEER-6 (2019) PIONEER-6 (2019) AWARD-CHN1 (2018) REWIND (2019) Inagaki et. al. 2012 DURATION-3 (2014) EXCEL (2017) DURATION-8 (2020) ELIXA (2015) HARMONEY-3 (2014) Harmony outcome (2018)	2 25 5 5 1 1 3 1 0 2 1 1 20 1 0 2 1 1 0 0 2 1 1 0 0 4 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0	439 957 632 4698 1501 1648 577 239 1395 410 1591 492 4943 215 223 7347 461 3031 3022 4717	0 0 0 16 0 4 4 0 0 0 0 1 1 2 0 1 2 1 1 1 1 1 1 1 1 1 1	219 487 212 4678 747 1649 290 204 409 1592 243 4949 212 223 7390 233 3032 710 4716				→ 1.53 → 1.68	[0.12; 72.21] [0.01; 8.14] [0.14; 7.14] [0.06; 37.12] [0.05; 5.51] [0.03; 19.16] [0.45; 35.77]	1.3% 1.5% 32.5% 1.4% 8.1% 1.3% 1.5% 3.0% 2.0% 1.4% 24.3% 1.0% 3.0% 4.0% 4.1% 1.3% 4.1% 1.3%
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 1.00$		36225		32741 0	.2	0.5	1 2	1.55 5	[1.08; 2.22]	100.0%

eFigure 3. Risks of the composite of gallbladder or biliary diseases, cholelithiasis, cholecystitis, and biliary diseases with GLP-1RAs compared with controls in trials in trials with treatment for diabetes

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; Cl, confidence interval.

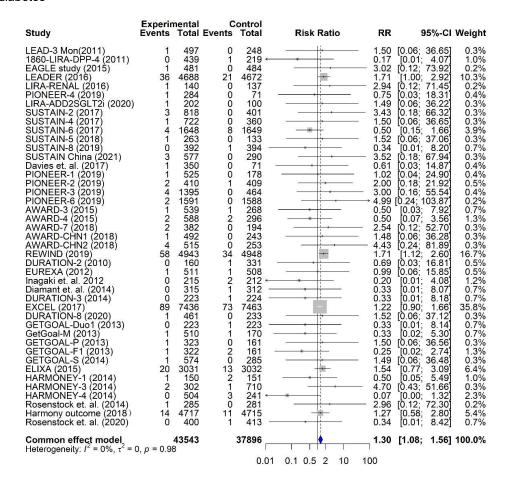
eFigure 3A. Risks of the composite of gallbladder or biliary diseases in patients with GLP-1RAs in trials with treatment for diabetes



eFigure 3B. Risks of cholelithiasis in patients with GLP-1RAs in trials with treatment for diabetes

Study	Experimental Events Total Ev	Control rents Total	Risk Ratio	RR	95%-CI Weight
LEAD-1 (2009) LEAD-4 (2009) Seino et al. (2010) LEAD-3 Mon (2011) 1860-LIRA-DPP-4 (2011) LEADER (2016) PIONEER-4 (2019) SUSTAIIN-1 (2017) SUSTAIN-1 (2017) SUSTAIN-1 (2017) SUSTAIN-6 (2017) Seino et al. (2017) Seino et al. (2018) Kaku et. al. (2018) Kaku et. al. (2018) SUSTAIN-6 (2019) PIONEER-1 (2019) PIONEER-3 (2019) PIONEER-3 (2019) PIONEER-4 (2019) PIONEER-8 (2015) AWARD-1 (2014) Ferdinand et. al. (2014) AWARD-3 (2015) AWARD-3 (2015) AWARD-6 (2015) AWARD-6 (2015) AWARD-6 (2015) AWARD-6 (2015) AWARD-7 (2015) AWARD-7 (2015) AWARD-1 (2018) REWIND (2019) Heine et. al. (2005) DURATION-2 (2010) EUREXA (2012) DURATION-8 (2020) GetGoal-M (2013) GETGOAL-S (2014) HARMONEY-3 (2014) HARMONEY-3 (2014) HARMONEY-4 (2014) Rosenstock et. al. (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) HARMONEY-4 (2014) Harmony outcome (2018) Common effect model Heterogeneity: I² = 0%, T² =	3 695 0 335 0 268 1 497 0 439 68 4688 1 284 4 258 1 605 3 722 58 1668 6 382 1 577 1 525 1 410 5 1395 1 285 1 577 1 525 1 410 5 1395 1 285 1 579 2 546 1 1 579 2 546 1 1 81 1 492 5 545 1 181 1 492 5 545 1 282 0 160 1 282 0 160 1 283 1 282 0 160 1 283 1 282 0 160 1 283 1 282 0 160 1 283 1 282 0 160 1 271 1 282 0 160 1 271 1 282 0 160 1 271 1 282 1 574 1 3 3031 0 302 1 574 1 3 90 1 2 7436 3 461 0 510 1 2 7436 3 461 0 510 1 2 7436 3 461 0 510 1 2 7436 3 461 0 510 1 2 771 4717 4717	2 346 1 175 1 132 0 248 1 219 50 4672 0 71 0 129 6 407 0 360 51 1669 0 103 0 133 0 120 3 394 0 290 0 178 1 409 2 466 0 71 4 1592 0 184 0 141 0 250 2 262 0 268 0 296 0 492 0 180 0 293 0 293 0 253 49 4949 0 267 1 331 0 508 2 224 73 7463 0 233 1 170 0 285 6 3032 2 710 0 241 0 392 7 4715		0.50 3.27 1.22 3.54 0.11 - 1.49 2.17 0.47 - 1.44 → 4.34 1.71	[0.13; 4.45] 0.9% [0.01; 4.26] 0.7% [0.01; 4.01] 0.2% [0.06; 36.65] 0.2% [0.01; 4.07] 0.7% [0.94; 1.95] 17.2% [0.94; 1.95] 17.2% [0.93; 1.90] 2.8% [0.23; 1.90] 2.8% [0.23; 1.90] 2.8% [0.79; 1.65] 17.6% [0.06; 36.77] 0.2% [0.18; 67.44] 0.2% [0.18; 57.47] 0.3% [0.18; 57.47] 0.3% [0.10; 2.77] 1.2% [0.06; 36.93] 0.2% [0.16; 4.29] 1.0% [0.06; 36.93] 0.2% [0.06; 36.93] 0.2% [0.06; 36.93] 0.2% [0.07; 3.39] 0.9% [0.10; 59.67] 0.2% [0.07; 3.39] 0.9% [0.10; 59.67] 0.2% [0.10
	Westernoon in	0.01	0.1 0.5 2 10	100	

eFigure 3C. Risks of cholecystitis in patients with GLP-1RAs in trials with treatment for diabetes

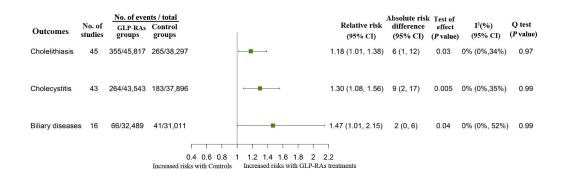


eFigure 3D. Risks of biliary diseases in patients with GLP-1RAs in trials with treatment for diabetes

Study	Experim			ontrol Total	ì	Risk Ratio	RR	95%-CI	Weight
1860-LIRA-DPP-4 (2011) LEADER (2016) SUSTAIN-6 (2017) SUSTAIN China (2021) PIONEER-3 (2019) PIONEER-2 (2019) PIONEER-6 (2019) AWARD-CHN1 (2018) REWIND (2019) Inagaki et al. 2012 DURATION-3 (2014) EXCEL (2017) DURATION-8 (2020) ELIXA (2015)	2 25 5 1 1 0 2 1 20 1 1 0 2	439 4698 1648 577 1395 410 1591 492 4943 215 223 7347 461 3031	0 16 4 0 0 12 0 12 0 2	219 ← 4678 1649 290 ← 466 ← 409 ← 1592 ← 2449 212 ← 223 ← 7390 ← 233 ← 3032 ←		Risk Ratio	1.56 1.25 1.51 1.00 0.33 2.00 1.48 1.67 2.96 0.33 1.01	[0.12; 51.79] [0.83; 2.91] [0.34; 4.65] [0.06; 36.93] [0.01; 8.14] [0.18; 22.05] [0.06; 36.28] [0.82; 3.41] [0.12; 72.21] [0.01; 8.14] [0.14; 7.14] [0.06; 37.12] [0.06; 37.12]	1.5% 35.0% 8.7% 1.5% 1.6% 3.3% 2.2% 1.1% 3.3% 4.4% 4.4%
HARMÓNEY-3 (2014) Harmony outcome (2018)	4	302 4717	1	710 ← 4716	-			[0.03; 19.16] [0.45; 35.77]	2.0% 2.2%
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$	0, p = 1.00	32489		31011 0.2	0.	5 1 2	1.47 5	[1.01; 2.15]	100.0%

eFigure 4. Overall risks of cholelithiasis, cholecystitis, and biliary diseases in patients with GLP-1RAs compared with controls in trials with treatment for diabetes

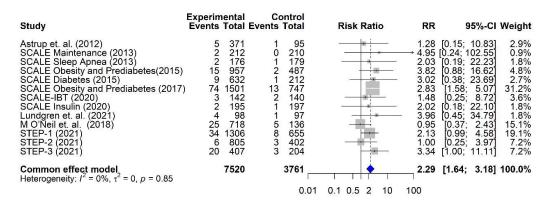
Notes: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidence interval. Absolute risk difference is the number of events per 10,000 people in a year.



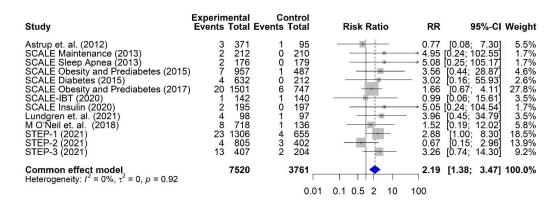
eFigure 5. Risks of the composite of gallbladder or biliary diseases, cholelithiasis, cholecystitis, and biliary diseases with GLP-1RAs compared with controls in trials with treatment for weight loss

Notes: A, risks of cholelithiasis; B, risks of cholecystitis; C, risks of biliary diseases. Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviation:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

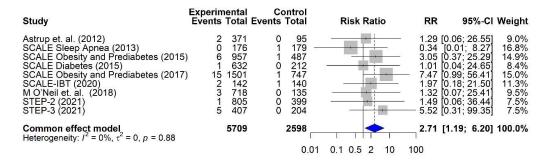
eFigure 5A. Risks of the composite of gallbladder or biliary diseases in patients with GLP-1RAs in trials with treatment for weight loss



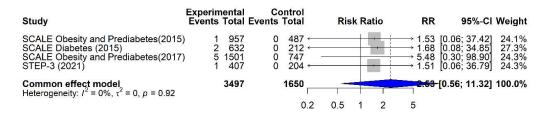
eFigure 5B. Risks of cholelithiasis in patients with GLP-1RAs in trials with treatment for weight loss



eFigure 5C. Risks of cholecystitis in patients with GLP-1RAs in trials with treatment for weight loss

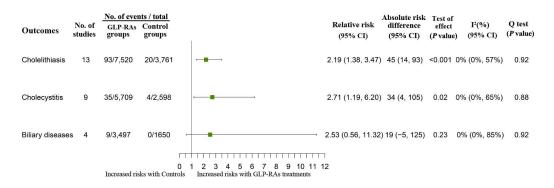


eFigure 5D. Risks of biliary diseases in patients with GLP-1RAs in trials with treatment for weight loss



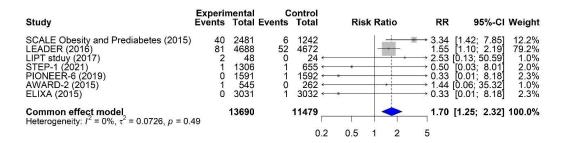
eFigure 6. Overall risks of cholelithiasis, cholecystitis and biliary diseases in patients with GLP-1RAs compared with controls in trials with treatment for weight loss

Notes: GLP-1RAs, glucagon-like peptide 1 receptor agonists; CI, confidence interval. Absolute risk difference is the number of events per 10,000 people in a year.



eFigure 7. Risks of cholecystectomy in patients with GLP-1RAs compared with controls

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.



eFigure 8. Risks of biliary tract cancer in patients with GLP-1RAs compared with controls

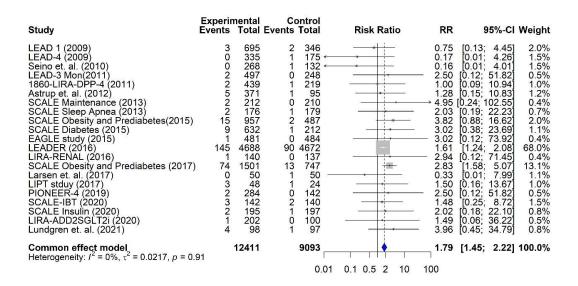
Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

Study	Experin Events		C Events	ontrol Total	Risk Ratio	RR	95%-CI	Weight
1860-LIRA-DPP-4 (2011) LEADER (2016) SCALE Obesity and Prediabetes (2017) SUSTAIN-6 (2017) PIONEER-6 (2019) REWIND (2019) EUREXA (2012) EXCEL (2017) GETGOAL-P (2013) ELIXA (2015) HARMONEY-5 (2015) Harmony outcome (2018)	161108150011	439 4688 1501 1648 1591 4943 511 7347 323 3031 271 4717	0 4 0 1 2 3 0 2 1 1 0 1	219 ← 4672 747 ← 1649 ← 1592 ← 4949 508 ← 7390 161 ← 3032 ← 392 ← 4715 ← 4715			[0.06; 36.63] [0.42; 5.29] [0.06; 36.62] [0.06; 15.98] [0.01; 4.17] [0.71; 10.06] [0.12; 73.04] [0.49; 12.96] [0.01; 4.06] [0.01; 8.18] [0.18; 106.07] [0.06; 15.98]	3.5% 20.8% 3.5% 5.2% 13.0% 15.6% 2.6% 10.4% 7.8% 2.1% 5.2%
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 0.86$		31010		30026		1.43	[0.80; 2.56]	100.0%

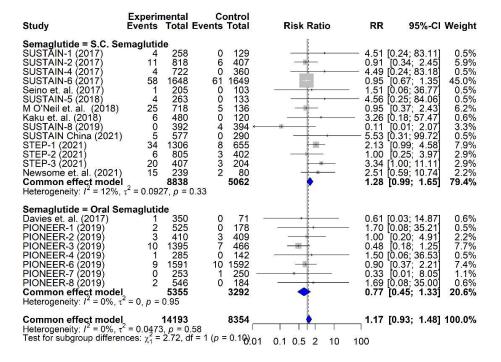
eFigure 9. Risks of gallbladder or biliary diseases in patients with different GLP-1RAs individuals compared with controls

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. The differences between individual GLP-1RAs were not significant (*P*-for interaction =0.07). **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

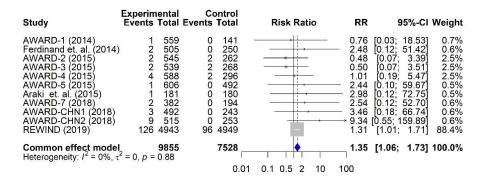
eFigure 9A. Association between gallbladder or biliary diseases and liraglutide



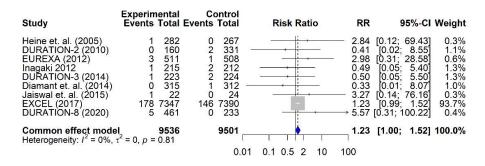
eFigure 9B. Association between gallbladder or biliary diseases and semaglutide



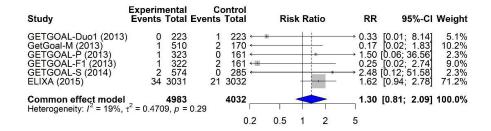
eFigure 9C. Association between gallbladder or biliary diseases and dulaglutide



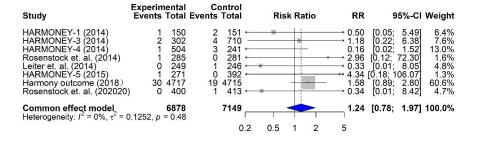
eFigure 9D. Association between gallbladder or biliary diseases and exenatide



eFigure 9E. Association between gallbladder or biliary diseases and lixisenatide

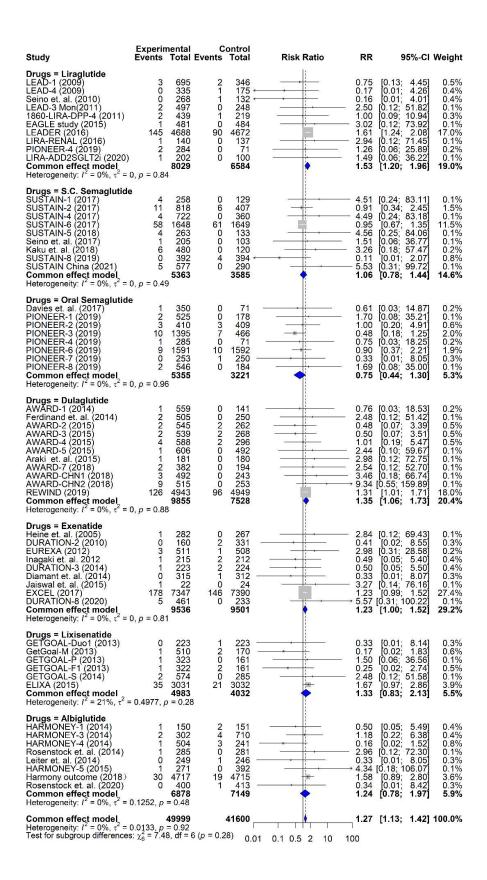


eFigure 9F. Association between gallbladder or biliary diseases and albiglutide



eFigure 10. Risks of gallbladder or biliary diseases with different GLP-1RAs medications compared with controls in trials with treatment for diabetes

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. Test for subgroup difference: The p values for interaction is 0.30. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists.



eFigure 11. Risks of gallbladder or biliary diseases with different GLP-1RAs medications compared with controls in trials for weight loss

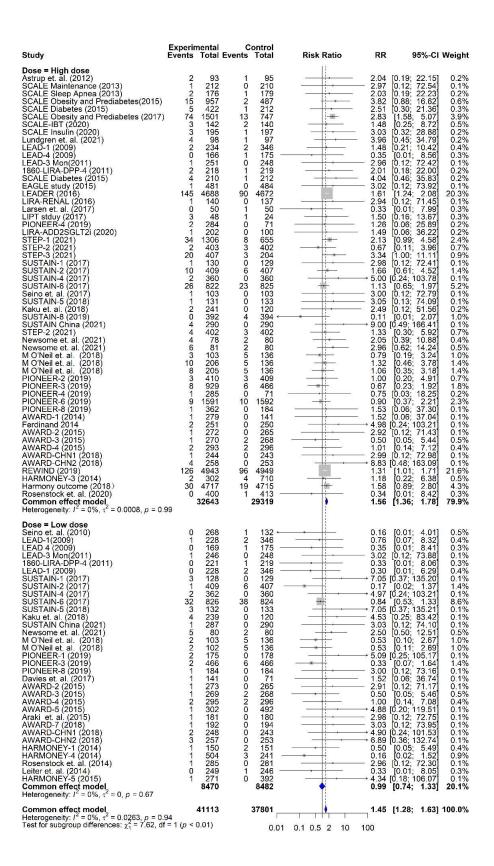
Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. Test for subgroup difference: The p values for interaction is 0.19. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists.

Study	Experimental (Events Total Event	Control s Total	Risk Ratio	RR	95%-CI Weight
Drugs = Liraglutide Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Sleep Apnea (2013) SCALE Diabetes (2015) SCALE Diabetes (2015) SCALE Diabetes (2015) SCALE Diabetes (2017) SCALE-IBT (2020) SCALE Insulin (2020) Lundgren et. al. (2021) Common effect model Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.99	2 176 15 957 9 632 74 1501 1	1 95 0 210 179 2 487 1 212 3 747 2 140 1 197 1 97 2364		→ 4.95 2.03 3.82 3.02 2.83 1.48 2.02	[0.15; 10.83] 2.9% [0.24; 102.55] 0.9% [0.19; 22.23] 1.8% [0.88; 16.62] 4.8% [0.38; 23.69] 2.7% [1.58; 5.07] 31.2% [0.25; 8.72] 3.6% [0.18; 22.10] 1.8% [0.45; 34.79] 1.8% [1.76; 4.36] 51.4%
Drugs = Semaglutide M O'Neil et. al. (2018) STEP-1 (2021) STEP-2 (2021) STEP-3 (2021) Common effect model Heterogeneity: I^2 = 17%, τ^2 = 0.0510, p = 0	34 1306 6 805 20 407 3236	5 136 8 655 3 402 3 204 1397	•	0.95 2.13 1.00 3.34 1.77	[0.37; 2.43] 15.1% [0.99; 4.58] 19.1% [0.25; 3.97] 7.2% [1.00; 11.11] 7.2% [1.09; 2.89] 48.6%
Common effect model Heterogeneity: l^2 = 0%, τ^2 = 0, p_0 = 0.85 Test for subgroup differences: χ_1^2 = 1.73, df	7520 = 1 (ρ = 0.19)	3761	0.1 0.5 2 10	2.29	[1.64; 3.18] 100.0%

eFigure 12. Effects of doses and duration of treatment on the association between GLP-1RAs and gallbladder or biliary diseases in all included trials

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** RR, relative risks; CI, confidential intervals; GLP-1RAs, glucagon-like peptide 1 receptor agonists; BMI, body mass index.

eFigure 12A. Effects of doses of GLP-1RAs treatments in all trials



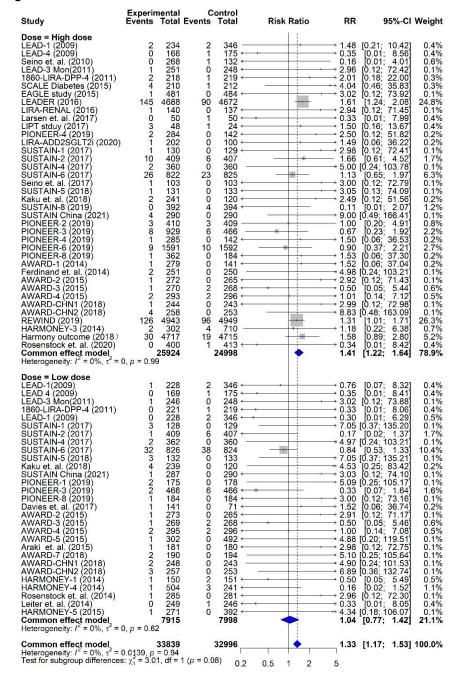
eFigure 12B . Effects of duration of GLP-1RAs treatments in all trials

Study	Experimental Events Total	Contro Events Tota		RR	95%-CI Weight
Duration = ≤ 26 weeks LEAD-1 (2009) LEAD-4 (2009) Seino et. al. (2010) EAGLE study (2015) LIRA-RENAL (2016) Larsen et. al. (2017) LIPT stduy (2017) LIPA-ADD2SGLT2i (2020) Davies et. al. (2017) PIONEER-1 (2014) Ferdinand et. al. (2014) AWARD-3 (2015) Araki et. al. (2015) AWARD-CHN1 (2018) Heine et. al. (2005) DURATION-2 (2010) DURATION-2 (2010) DURATION-3 (2010) GETGOAL-F1 (2013) GETGOAL-F1 (2013) GETGOAL-F1 (2014) Rosenstock et. al. (2020) Common effect model Heterogeneity: I² = 0%, τ² = 0, ρ = 0.97	3 695 0 335 0 268 1 481 1 140 0 50 3 48 1 202 1 350 2 525 1 559 2 505 2 539 1 181 3 492 1 282 0 123 0 223 0 223 1 510 1 323 1	2 344 1 17: 1 13: 0 48- 0 13: 1 5: 1 2: 0 10: 0 17: 0 14: 0 25: 2 26: 0 26: 0 26: 0 26: 0 26: 1 22: 2 17: 0 16: 2 16: 0 16: 2 16: 0 26: 1 22: 1 22: 2 17: 0 16: 0 16: 0 26: 1 26: 1 27: 1		1.49 0.61 1.70 0.76 0.50 2.48 0.50 2.98 0.20 0.33 0.17 1.50 0.25 0.25 	[0.13; 4.45] 0.4% [0.01; 4.26] 0.3% [0.01; 4.01] 0.3% [0.01; 4.01] 0.3% [0.12; 73.92] 0.1% [0.01; 7.99] 0.3% [0.01; 7.99] 0.3% [0.06; 36.22] 0.1% [0.06; 36.22] 0.1% [0.03; 14.87] 0.1% [0.07; 3.51] 0.1% [0.07; 3.51] 0.4% [0.12; 51.42] 0.1% [0.07; 3.51] 0.4% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.01; 4.16] 0.4% [0.01; 4.16] 0.4% [0.01; 8.14] 0.3% [0.01; 4.16] 0.4% [0.01; 8.14] 0.3% [0.01; 8.14] 0.3% [0.01; 8.14] 0.3% [0.01; 8.14] 0.3% [0.01; 8.15] 0.5% [0.01; 8.14] 0.4% [0.01; 8.14] 0.4% [0.01; 8.14] 0.4% [0.01; 8.14] 0.4% [0.01; 8.14] 0.4% [0.01; 8.14] 0.5% [0.01; 8.14] 0.5% [0.01; 8.14] 0.2% [0.01; 8.14] 0.5% [0.01; 8.14] 0.5% [0.01; 8.14] 0.5% [0.01; 8.14] 0.5% [0.01; 8.14] 0.5% [0.01; 8.15] 0.5%
Duration = >26 weeks LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Sleep Apnea (2013) SCALE Obesity and Prediabetes (2015) LEADER (2016) SCALE Diabetes (2015) LEADER (2016) SCALE Obesity and Prediabetes (2017) PIONEER-4 (2019) SCALE Insulin (2020) Lundgren et. al. (2021) SUSTAIN-1 (2017) SUSTAIN-1 (2017) SUSTAIN-2 (2017) SUSTAIN-4 (2017) SUSTAIN-5 (2018) Seino et. al. (2018) Kaku et. al. (2018) Kaku et. al. (2018) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-1 (2017) SUSTAIN-9 (2018) Kaku et. al. (2018) Kaku et. al. (2018) FEP-1 (2021) STEP-1 (2021) STEP-1 (2021) STEP-3 (2021) STEP-3 (2021) Newsome et. al. (2021) PIONEER-3 (2019) PIONEER-4 (2019) PIONEER-4 (2019) PIONEER-6 (2019) PIONEER-7 (2019) PIONEER-8 (2019) PIONEER-8 (2019) AWARD-5 (2015) AWARD-5 (2015) AWARD-5 (2015) AWARD-5 (2015) AWARD-5 (2015) AWARD-6 (2012) Inagaki et. al. (2014) Diamant et. al. (2014) Diamant et. al. (2014) Diamant et. al. (2014) HARMONEY-1 (2014) HARMONEY-3 (2014) HARMONEY-1 (2014) HARMONEY-1 (2014) HARMONEY-3 (2014) HARMONEY-3 (2014) HARMONEY-5 (2015) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-7 (2014) HARMONEY-7 (2015) HARMONEY-7 (2014) HARMONEY-6 (2015) HARMONEY-7 (2015) HARMONEY-7 (2014) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-7 (2014) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-7 (2014) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-6 (2015) HARMONEY-7 (2014) HARMONEY-6 (2015) HARMONEY-6 (2015	9 032 145 4688 7) 74 1501 2 284 3 142 2 195 4 98 4 258 11 818 4 722 58 1648 4 722 58 1648 4 263 1 205 25 577 34 1306 6 6 480 0 392 5 577 34 1306 6 6 480 0 392 1 225 5 577 34 1306 6 6 480 1 225 5 577 34 1306 6 6 480 1 225 5 577 3 4 1306 6 6 480 1 225 5 577 3 4 1306 6 6 480 1 225 5 5 77 3 4 1306 1 285 9 515 1 225 1 225 1 225 1 225 1 225 1 285 2 382 9 515 1 225 1 226 1 227 1 226 1 227 1 226 1 227 1 226 1 227 1 226 1 227 1 228 1 228 1 229 1 229	0 244 1 21s 1 21s 1 290 2 487 2 488 2 481 0 144 2 144 1 199 0 467 1 3 744 2 144 1 199 0 366 61 1644 0 133 0 103 0 103 0 103 0 103 1 225 1 340 1 255 2 26 2 2 88 3 400 3 200 2 88 655 1 10 159 1 255 2 26 2 29 3 47 1 50 3 24 1 50 3 3 24 1 50 3 50 3 50 3 50 3 50 3 50 3 50 3 50 3		1.28	(0.12; 51.82] 0.1% (0.09; 10.94] 0.2% (0.15; 10.83] 0.3% (0.19; 22.23] 0.2% (0.88; 16.62] 0.4% (0.88; 16.62] 0.4% (0.38; 23.69] 0.3% [1.24; 2.08] 15.1% (1.58; 5.07] 2.9% (0.12; 51.82] 0.1% (0.25; 8.72] 0.3% (0.25; 8.72] 0.3% (0.45; 34.79] 0.2% (0.45; 34.79] 0.2% (0.45; 34.79] 0.2% (0.45; 34.79] 0.2% (0.24; 83.18] 0.1% (0.67; 1.35] 10.2% (0.25; 84.06] 0.1% (0.67; 1.35] 10.2% (0.25; 84.06] 0.1% (0.19; 2.43] 1.4% (0.19; 2.43] 1.4% (0.19; 2.43] 1.4% (0.19; 2.43] 1.4% (0.19; 2.43] 1.4% (0.19; 3.72] 0.1% (0.19; 3.72] 0.1% (0.19; 3.72] 0.1% (0.10; 10.74] 0.5% (0.10; 10.74] 0.5% (0.10; 10.74] 0.5% (0.10; 11.11] 0.7% (0.10; 10.74] 0.5% (0.10; 10.74] 0.5% (0.11; 1.71] 16.1% (0.12; 52.70] 0.1% (1.10; 1.71] 16.1% (0.11; 1.71] 16.1% (0.11; 1.71] 16.1% (0.12; 52.70] 0.1% (1.10; 15.54] 0.1% (1.10; 1.71] 16.1% (0.11; 1.71] 16.1
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0252$, $p = 0$ Test for subgroup differences: $\chi_1^2 = 4.68$,	0.85		1.01 0.1 0.5 2 10	100	boones, among the second

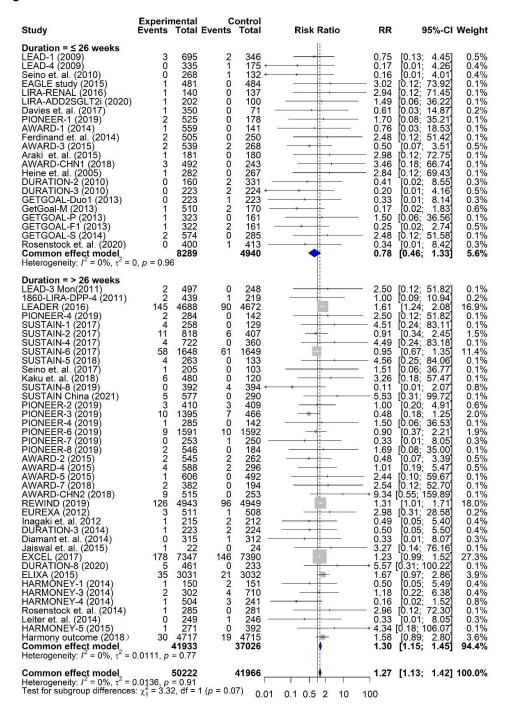
eFigure 13. Effects of doses and duration of treatment on the risks of gallbladder or biliary diseases in trials with treatment for diabetes

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals.

eFigure 13A. Effects of doses of GLP-1RAs treatments in trials with treatment for diabetes



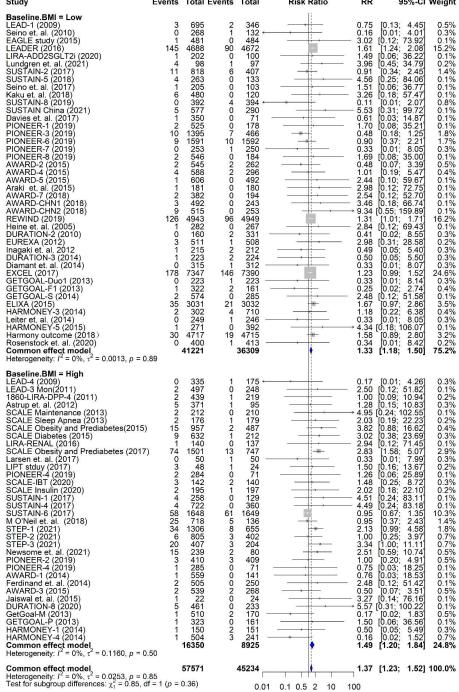
eFigure 13B. Effects of duration of GLP-1RAs treatments in trials with treatment for diabetes



eFigure 14. Effects of baseline BMI and types of control on the association between GLP-1RAs and gallbladder or biliary diseases

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. Abbreviations: GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals; BMI, body mass index. eFigure 15A. Effects of baseline BMI in all trials

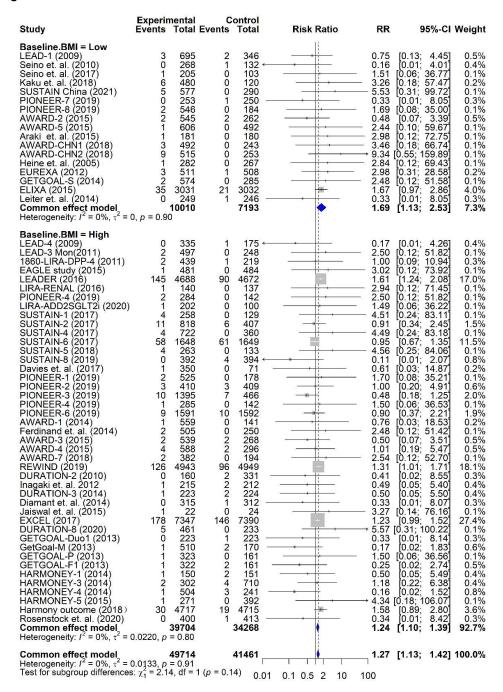




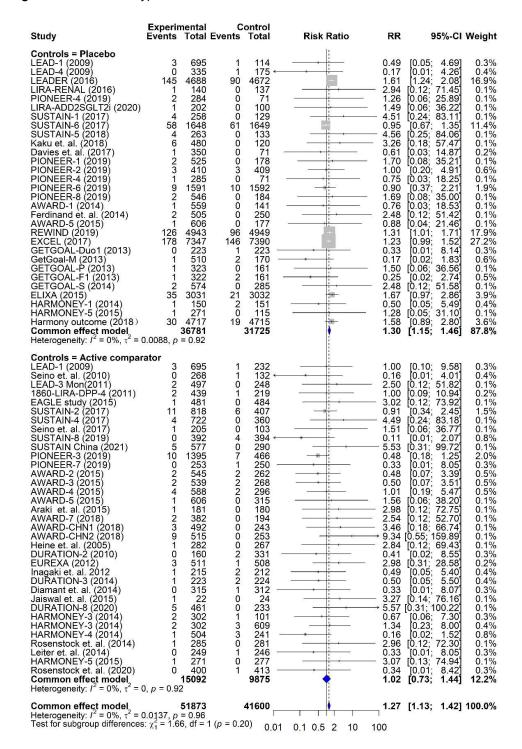
eFigure 14B. Effects of types of control in all trials

Study	Experimenta Events Tota		ontrol Total	Risk Ratio	RR	95%-CI V	Veight
Controls = Placebo LEAD-1 (2009) LEAD-4 (2009) Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Sleep Apnea (2013) SCALE Diesbety and Prediabetes (2015) SCALE Diesbetes (2015) LEADER (2016) LIRA-RENAL (2016) SCALE Obesity and Prediabetes (2017 LIPT stduy (2017) LIPT stduy (2017) PIONEER-4 (2019) SCALE-IBT (2020) SCALE Insulin (2020) LIRA-ADD2SGLT2i (2020) LIRA-BDD2SGLT2i (2020) LURA-BDD2SGLT2i (2020) LURA-BDD2SGLT2i (2020) LURA-BD10SGLT2i (2019) SUSTAIN-5 (2017) SUSTAIN-5 (2018) M O'Neil et al. (2018) Kaku et. al. (2018) Kaku et. al. (2018) STEP-1 (2021) STEP-2 (2021) STEP-2 (2021) STEP-2 (2021) Newsome et. al. (2017) PIONEER-1 (2019) PIONEER-1 (2019) PIONEER-2 (2019) PIONEER-4 (2019) PIONEER-8 (2019) PIONEER-8 (2019) AWARD-1 (2014) Ferdinand et. al. (2014) AWARD-5 (2015) REWIND (2019) EXCEL (2017) GETGOAL-Duo1 (2013) GETGOAL-P (2013) GETGOAL-P (2013) GETGOAL-P (2014) HARMONEY-1 (2014) HARMONEY-5 (2015) HARMONEY-5 (2015) HARMONEY-5 (2015) HARMONEY-5 (2015) HARMONEY-5 (2015) Common effect model Heterogeneity: I² = 0%, x² = 0.0262, p = 0	34 1306 6 807 20 407 115 233 1 3506 2 525 3 411 1 288 9 1597 2 507 1 600 126 4943 1 7344 0 223 1 516 1 322 2 577 35 3031 1 1506 1 271 30 4711 344638	1 0 0 1 2 1 0 0 0 1 2 1 0 0 1 0 1 0 1 0	114 175 98 210 179 487 212 4672 137 747 50 24 137 747 100 97 1140 197 129 1649 133 120 204 80 71 1592 204 80 71 1592 184 409 71 1592 184 409 133 120 1555 402 164 1555 402 164 1555 402 164 1555 402 164 161 161 161 161 161 161 161 161 161		2.03 3.82 1.61 2.94 2.83 0.33 1.50 1.28 2.02 1.48 2.02 1.49 0.95 4.56 0.95 3.26 2.13 1.00 3.34 2.51 1.00 0.75 0.95 1.00 0.75 0.95 1.23 0.33 0.33 0.33 0.33 0.33 0.33 0.33 0	[0.99; 1.52] [0.01; 8.14] [0.02; 1.83] [0.06; 36.56] [0.02; 2.74] [0.12; 51.58] [0.97; 2.86] [0.05; 5.49] [0.05; 31.10] [0.89; 2.80]	0.3% 0.3% 0.1% 0.2% 0.4% 0.3% 15.1% 2.9% 0.2% 0.1% 0.2% 0.1% 0.2% 0.1% 0.1% 0.1% 0.1% 0.1% 0.1% 0.1% 0.1
Controls = Active comparator LEAD-1 (2009) Seino et. al. (2010) LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) EAGLE study (2015) SUSTAIN-8 (2017) SUSTAIN-8 (2017) SUSTAIN-8 (2017) SUSTAIN-8 (2019) SUSTAIN China (2021) PIONEER-7 (2019) PIONEER-7 (2019) PIONEER-7 (2019) AWARD-3 (2015) AWARD-3 (2015) AWARD-3 (2015) AWARD-3 (2015) AWARD-6 (2015) AWARD-6 (2015) AWARD-7 (2018) AWARD-7 (2018) AWARD-CHN1 (2018) AWARD-CHN2 (2018) Beine et. al. (2015) DURATION-9 (2010) EUREXA (2012) Inagaki et. al. (2014) Jaiswal et. al. (2014) Jaiswal et. al. (2014) Jaiswal et. al. (2014) HARMONEY-3 (2014) HARMONEY-3 (2014) HARMONEY-4 (2014) Rosenstock et. al. (2014) HARMONEY-5 (2015) ROSENSTOCK et. al. (2020) Common effect model Heterogeneity: I² = 0%, r² = 0.0239, p = 0 Test for subgroup differences: χ² = 3.00, d	3 698 2 493 2 493 2 493 1 488 11 818 4 722 6 0 392 6 5 577 10 1398 0 255 2 54 2 2 53 4 588 1 606 1 181 2 382 3 492 2 533 4 528 1 288 1 222 5 46 1 288 0 166 3 511 1 212 0 311 1 22 5 466 1 2 302 2 302 2 302 1 524	101106000407122220000002122100013300101	232	0.1 0.5 2 10	1.00 1.28 3.02 0.449 1.51 0.11 5.53 0.48 0.33 0.48 0.50 1.01 2.98 2.98 2.346 2.98 2.98 2.57 3.46 0.49 0.50 0.33 3.77 1.34 0.49 0.50 1.01 1.0	[0.10; 9.58] [0.01; 4.01] [0.12; 51.82] [0.09; 10.94] [0.15; 10.83] [0.12; 73.92] [0.34; 2.45] [0.24; 83.18] [0.06; 36.77] [0.01; 2.07] [0.18; 1.25] [0.18; 1.25] [0.01; 3.51] [0.07; 3.51] [0.07; 3.51] [0.07; 3.51] [0.07; 3.51] [0.06; 38.20] [0.07; 3.51] [0.12; 72.75] [0.12; 52.70] [0.12; 52.70] [0.12; 52.70] [0.12; 52.70] [0.12; 52.70] [0.12; 52.70] [0.12; 52.70] [0.12; 69.43] [0.02; 8.58] [0.31; 28.58] [0.31; 28.58] [0.31; 28.58] [0.31; 28.58] [0.31; 28.58] [0.05; 5.50] [0.02; 3.80] [0.01; 8.07] [0.06; 7.30] [0.02; 1.52] [0.06; 7.30] [0.01; 8.05] [0.01; 8.42] [0.74; 1.44]	0.3% 0.3% 0.1% 0.3% 0.11% 0.3% 0.11% 0.1% 0.1% 0.1% 0.1% 0.1% 0.1% 0.

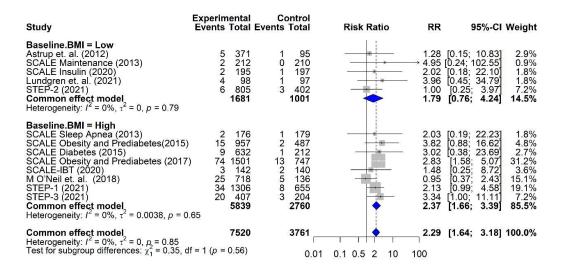
eFigure 14C. Effects of baseline BMI in trials with treatment for diabetes



eFigure 14D. Effects of types of control in trials with treatment for diabetes



eFigure 14E. Effects of baseline BMI in trials with treatment for weight loss



eFigure 14F. Effects of types of control in trials with treatment for weight loss

Study	Experimental Events Total Even	Control ts Total	Risk Ratio	RR	95%-CI Weight
Controls = Placebo Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Sleep Apnea (2013) SCALE Desity and Prediabetes (2015) SCALE Diabetes (2015) SCALE Diabetes (2015) SCALE Insulin (2020) Lundgren et. al. (2021) M O'Neil et. al. (2018) STEP-1 (2021) STEP-2 (2021) STEP-2 (2021) STEP-3 (2021) Common effect model Heterogeneity: I ² = 0%, r ² = 0, p = 0.86	9 632 74 1501 3 142 2 195 4 98 25 718 34 1306 6 805	0 98 0 210 1 179 2 487 1 212 3 747 2 140 1 197 1 97 5 136 3 402 3 204 3764		4.95 [0 2.03 [0 3.82 [0 3.82 [0 2.83 [1 1.48 [0 2.02 [0 3.96 [0 2.13 [0 3.34 [1	.16; 52.30] 1.4% 24; 102.55] 0.9% .19; 22.23] 1.8% .88; 16.62] 4.7% .158; 5.07] 30.7% .25; 8.72] 3.6% .45; 34.79] 1.8% .45; 34.79] 1.8% .45; 34.79] 1.8% .99; 4.58] 18.9% .25; 3.97] 7.1% .00; 11.11] 7.1% .66; 3.24] 97.2%
Controls = Active comparator Astrup et. al. (2012) Common effect model Heterogeneity: not applicable	5 371 371	1 95 95			.15; 10.83] 2.8% .15; 10.83] 2.8%
Common effect model Heterogeneity: $l^2 = 0\%$, $\tau^2 = 0$, $p = 0.89$ Test for subgroup differences: $\chi_1^2 = 0.29$, or	7891 If = 1 (ρ = 0.59)	3859	0.1 0.5 2 10	2.30 [1	.65; 3.19] 100.0%

eFigure 15. Effects of types of trials on the risks of gallbladder or biliary diseases in trials with treatment for diabetes

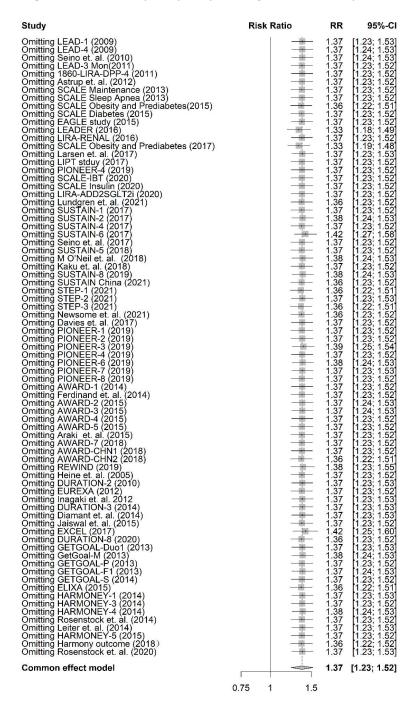
Notes: Experimental, GLP-1RAs treatments; Control, placebo or active comparators. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risks; CI, confidential intervals.

Study	Experimental Events Total Ev	Control vents Total	Risk Ratio	RR	95%-CI Weight
Types.of.trials = Non-CV0 LEAD-1 (2009) LEAD-1 (2009) Seino et. al. (2010) LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) EAGLE study (2015) LIRA-RENAL (2016) PIONEER-4 (2019) LIRA-ADD2SGLT2i (2020) SUSTAIN-1 (2017) SUSTAIN-2 (2017) SUSTAIN-5 (2018) Seino et. al. (2017) SUSTAIN-5 (2018) Seino et. al. (2017) Kaku et. al. (2018) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-8 (2019) PIONEER-1 (2019) PIONEER-3 (2019) PIONEER-3 (2019) PIONEER-4 (2019) PIONEER-8 (2019) PIONEER-8 (2019) PIONEER-8 (2019) PIONEER-8 (2019) AWARD-1 (2014) AWARD-1 (2014) AWARD-1 (2014) AWARD-1 (2015) DURATION-2 (2010) EUREXA (2012) Inagaki et. al. (2014) Jaiswal et. al. (2014) Jaiswal et. al. (2014) Jaiswal et. al. (2014) Jaiswal et. al. (2013) GETGOAL-S (2013) GETGOAL-F (2013) GETGOAL-F (2013) GETGOAL-F (2013) GETGOAL-F (2014) HARMONEY-1 (2014) HARMONEY-1 (2014) HARMONEY-3 (2014) HARMONEY-3 (2014) HARMONEY-3 (2014) HARMONEY-5 (2015) Rosenstock et. al. (2020) Common effect model Heterogeneity: I ² = 0%, x ² =	3 695 0 335 0 268 2 497 2 439 1 481 1 140 2 284 1 202 4 258 1 818 4 722 4 265 6 480 0 392 5 577 1 350 2 525 3 410 10 1395 1 285 0 253 2 546 1 559 2 505 2 545 2 545 1 181 2 382 3 9 515 1 282 3 4 588 1 606 1 181 2 382 3 9 515 1 282 3 4 588 1 606 3 511 1 223 0 315 1 227 1 504 1 500 2 302	2 346 1 175 ← 1 1 132 ← 1 0 248 1 219 0 484 0 137 0 71 0 100 0 129 6 360 0 133 0 103 0 120 4 394 ← 1 0 290 0 171 0 184 0 290 0 184 0 141 0 250 2 262 2 268 2 268 2 296 0 184 0 194 0 250 2 2 262 2 268 2 296 2 2 268 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2 2		0.41 2.98 0.49 0.33 — 3.27 → 5.57 0.33 0.17 - 1.50 0.25 — 2.48 0.50	[0.13; 4.45] 0.5% [0.01; 4.26] 0.4% [0.01; 4.01] 0.4% [0.02; 51.82] 0.1% [0.12; 73.92] 0.1% [0.12; 73.92] 0.1% [0.12; 73.92] 0.2% [0.06; 36.22] 0.1% [0.06; 36.22] 0.1% [0.34; 2.45] 1.5% [0.24; 83.18] 0.1% [0.25; 84.06] 0.1% [0.06; 36.77] 0.8% [0.06; 36.77] 0.8% [0.06; 36.77] 0.8% [0.06; 36.77] 0.1% [0.08; 35.747] 0.2% [0.01; 2.07] 0.8% [0.03; 14.87] 0.2% [0.03; 14.87] 0.2% [0.03; 18.25] 0.3% [0.08; 35.21] 0.1% [0.08; 35.21] 0.1% [0.07; 3.39] 0.5% [0.08; 35.01] 0.1% [0.08; 35.01] 0.1% [0.07; 3.39] 0.5% [0.01; 51.42] 0.1% [0.07; 3.51] 0.5% [0.07; 3.51] 0.5% [0.12; 51.42] 0.1% [0.07; 3.51] 0.5% [0.12; 51.42] 0.1% [0.07; 3.51] 0.5% [0.12; 51.42] 0.1% [0.01; 59.67] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.01; 59.67] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.01; 59.67] 0.1% [0.12; 51.42] 0.1% [0.01; 59.67] 0.1% [0.12; 51.58] 0.1% [0.12; 51.59.89] 0.1% [0.12; 69.43] 0.1% [0.01; 8.58] 0.2% [0.01; 8.58] 0.4% [0.02; 1.52] 0.8% [0.02; 1.52] 0.8% [0.02; 1.52] 0.8% [0.01; 8.14] 0.3% [0.02; 1.52] 0.8% [0.01; 8.14] 0.3% [0.02; 1.52] 0.8% [0.01; 8.05] 0.3% [0.01; 8.07] 0.3% [0.01
Types.of.trials = CVOTs LEADER (2016) SUSTAIN-6 (2017) PIONEER-6 (2019) REWIND (2019) EXCEL (2017) ELIXA (2015) Harmony outcome (2018) Common effect model Heterogeneity: $l^2 = 22\%$, $\tau^2 = 100$	145 4688 58 1648 9 1591 126 4943 178 7347 35 3031 30 4717 27965 = 0.0100, p = 0.26	90 4672 61 1649 10 1592 96 4949 146 7390 21 3032 19 4715 27999		1.61 0.95 0.90 1.31 1.23 1.67 1.58 1.31	[1.24; 2.08] 17.0% [0.67; 1.35] 11.5% [0.37; 2.21] 1.9% [1.01; 1.71] 18.0% [0.99; 1.52] 27.4% [0.97; 2.86] 3.9% [0.89; 2.80] 3.6% [1.16; 1.48] 83.2%
Common effect model Heterogeneity: $I^2 = 0\%$, $\tau^2 =$ Test for subgroup difference	49999 0.0133, <i>p</i> = 0.92 s: χ ₁ ² = 1.93, df = 1 (<i>p</i>	41600 p = 0.16) 0.01	0.1 0.5 2 10	1.27	[1.13; 1.42] 100.0%

eFigure 16. Sensitivity analyses by omitting each trial one by one and removing studies with albiglutide

Abbreviations: GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval Experimental, GLP-1RAs treatments; Control, placebo or active control.

eFigure 17A. Sensitivity analysis by omitting each trial one by one



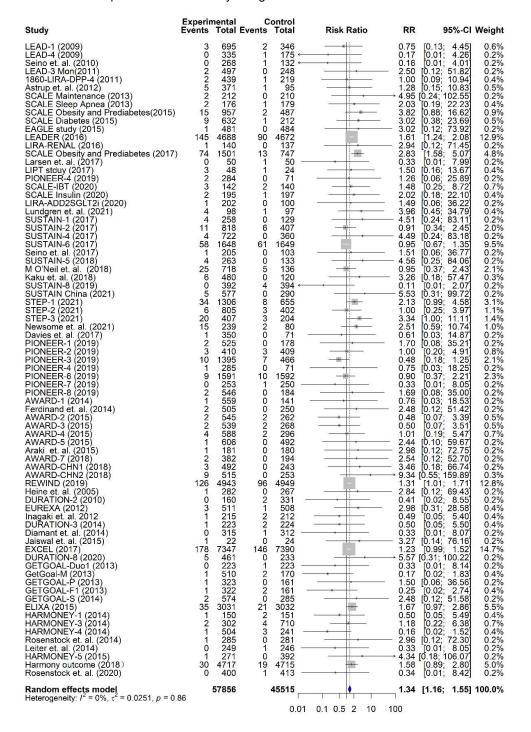
eFigure 16B. Sensitivity analysis by removing studies with albiglutide

Study	Experin Events			ontrol Total	Risk Ratio	RR	95%-CI Weight
LEAD-1 (2009) LEAD-4 (2009) Seino et. al. (2010) LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Obesity and Prediabetes(2015) SCALE Diabetes (2015) EAGLE study (2015) LEADER (2016) LIRA-RENAL (2016) SCALE Obesity and Prediabetes (2017) LIPT stduy (2017) LIPT stduy (2017) LIPT stduy (2017) LIPT stduy (2017) PIONEER-4 (2019) SCALE Insulin (2020) SCALE Insulin (2020) SCALE Insulin (2020) SCALE Insulin (2020) SCALE Insulin (2021) SUSTAIN-1 (2017) SUSTAIN-1 (2017) SUSTAIN-2 (2017) SUSTAIN-5 (2018) M O'Neil et. al. (2017) SUSTAIN-8 (2019) SUSTAIN China (2021) STEP-1 (2021) STEP-2 (2021) STEP-3 (2021) STEP-3 (2021) Newsome et. al. (2017) PIONEER-1 (2019) PIONEER-2 (2019) PIONEER-3 (2019) PIONEER-4 (2019) PIONEER-8 (2019) PIONEER-8 (2019) PIONEER-8 (2019) PIONEER-8 (2019) AWARD-1 (2014) Ferdinand et. al. (2015) AWARD-5 (2015) AWARD-5 (2015) AWARD-7 (2018) AWARD-7 (2018) AWARD-7 (2018) AWARD-7 (2018) AWARD-7 (2019) PIONEEXA (2012) Inagaki et. al. (2015) AWARD-7 (2018) AWARD-7 (2019) PIONEEXA (2012) Inagaki et. al. (2015) EXCEL (2017) DURATION-3 (2014) Jaiswal et. al. (2015) EXCEL (2017) DURATION-8 (2020) GETGOAL-P (2013)	0323214411485142605346205123019021222241123996103111018501111235	695 3355 2688 497 439 37112 1757 439 3212 1757 439 37112 1757 481 140 150 161 150 161 150 161 161 161 161 161 161 161 161 161 16	21110112100903111021010606100504408332000377010110000222200000960212221066012002021	346 175 ± 248 219 95 210 179 487 212 484 4672 137 747 100 97 129 407 360 1649 103 133 136 120 407 407 407 408 409 409 409 409 409 409 409 409		→ 4.951 - 2.943 - 3.02 - 3.02 - 3.02 - 3.02 - 1.294 - 3.96 - 4.51 - 4.95 - 4.51 - 4.51 - 4.51 - 0.91 - 3.261 - 1.50 - 3.261 - 1.70 0.95 - 3.34 - 2.513 0.75 0.90 - 3.449 - 3.96 - 3.97 - 3.	[0.13; 4.45] 0.5% [0.01; 4.26] 0.4% [0.01; 4.01] 0.4% [0.02; 51.82] 0.1% [0.09; 10.94] 0.2% [0.15; 10.83] 0.3% 0.24; 102.55] 0.1% [0.19; 22.23] 0.2% [0.18; 16.62] 0.5% [0.38; 23.69] 0.3% [0.12; 73.92] 0.1% [1.24; 2.08] 16.0% [0.12; 71.45] 0.1% [0.01; 79.9] 0.3% [0.16; 13.67] 0.2% [0.16; 13.67] 0.2% [0.16; 13.67] 0.2% [0.06; 25.89] 0.1% [0.25; 8.72] 0.4% [0.26; 8.72] 0.4% [0.26; 83.11] 0.1% [0.26; 84.06] 0.1% [0.31; 22.10] 0.2% [0.06; 36.22] 0.1% [0.34; 24.5] 1.4% [0.67; 1.35] 10.9% [0.34; 24.5] 1.5% [0.36; 24.5] 1.5% [0.37; 2.43] 1.5% [0.18; 57.47] 0.1% [0.31; 99.72] 0.1% [0.39; 4.58] 1.9% [0.25; 3.97] 0.7% [0.31; 99.72] 0.1% [0.99; 4.58] 1.9% [0.25; 3.97] 0.7% [0.31; 99.72] 0.1% [0.99; 4.58] 1.9% [0.25; 3.97] 0.7% [0.31; 99.72] 0.1% [0.99; 4.58] 1.9% [0.25; 3.97] 0.7% [0.11; 57.47] 0.15% [0.08; 35.20] 0.1% [0.08; 35.20] 0.1% [0.08; 35.20] 0.1% [0.09; 5.47] 0.5% [0.19; 54.47] 0.5% [0.19; 54.47] 0.5% [0.19; 54.47] 0.5% [0.19; 54.47] 0.5% [0.19; 54.47] 0.5% [0.19; 54.47] 0.5% [0.19; 55.47] 0.5% [0.19; 55.47] 0.5% [0.19; 55.47] 0.5% [0.19; 55.47] 0.5% [0.19; 55.47] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 51.42] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 52.70] 0.1% [0.12; 51.58] 0.2% [0.05; 5.50] 0.4% [0.05; 5.50] 0.4% [0.07; 3.51] 0.5% [0.07; 3.51] 0.5% [0.07; 3.51] 0.5% [0.09; 1.52] 25.9
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0.0312$, $\rho = 0$.	84			0.0	1 0.1 0.5 2 10	100	

eFigure 17. Sensitivity analyses by using random-effect models

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

eFigure 17A. Risks of the composite of gallbladder or biliary diseases with GLP-1RAs treatments compared with controls by using random-effect models



eFigure 17B. Risks of cholelithiasis with GLP-1RAs treatments compared with controls by using random-effect models

Study	Experir Events		C Events	ontrol Total	Risk Ratio	RR	95%-Cl Weight
LEAD-1 (2009) LEAD-4 (2009) Seino et. al. (2010) LEAD-3 Mon (2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) SCALE Maintenance (2013) SCALE Sleep Apnea (2013) SCALE Diabetes (2015) LEADER (2016) SCALE Diabetes (2015) LEADER (2016) SCALE Obesity and Prediabetes (2017) LIPT stduy (2017) Larsen et. al. (2017) PIONEER-4 (2019) SCALE Insulin (2020) SCALE Insulin (2020) SCALE Insulin (2020) SCALE Insulin (2021) SUSTAIN-1 (2017) SUSTAIN-1 (2017) SUSTAIN-2 (2017) SUSTAIN-5 (2017) SUSTAIN-6 (2017) SUSTAIN-8 (2017) SUSTAIN-9 (2017) SUSTAIN-1 (2018) M O'Neil et. al. (2018) Kaku et. al. (2018) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-9 (2011) STEP-1 (2021) STEP-1 (2021) STEP-1 (2021) STEP-2 (2021) STEP-3 (2021) PIONEER-4 (2019) PIONEER-4 (2019) PIONEER-6 (2019) PIONEER-6 (2019) PIONEER-6 (2019) PIONEER-6 (2015) AWARD-1 (2014) AWARD-3 (2015) AWARD-5 (2015) AWARD-5 (2015) AWARD-6 (2017) DURATION-8 (2020) GEGOAL-8 (2014) HARMONEY-9 (2014) HARMONEY-9 (2014) HARMONEY-9 (2014) HARMONEY-9 (2014) HARMONEY-9 (2014) HARMONEY-9 (2014) HARMONEY-4 (2014) Random effects more	4 68	695 3358 4497 4371 121757 6881 497 4051 4051 4051 4051 4051 4051 4051 4051	2111011100105661110101060510010300043201204000200000009901020301062007	346 175 ← 132 ← 248 219 9 9 9 9 10 179 487 212 4672 747 140 197 129 407 103 133 136 133 136 120 80 655 402 204 178 406 71 1592 184 141 1592 184 141 1592 184 141 250 262 228 492 184 178 293 494 747 1592 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 184 1793 1794 1794 1794 1794 1794 1795 1794 1795		0.17 0.17 0.77 4.95 3.56 3.02 1.36 1.50 0.39 3.96 4.51 0.99 3.49 1.51 3.55 1.52 3.26 0.14 1.52 3.288 0.67 3.288 0.75 1.69 0.76 2.88 0.75 1.69 0.76 2.88 0.75 1.69 0.76 2.88 0.75 1.69 0.76 2.88 0.75 1.69 0.76 2.88 0.75 1.69 0.76 2.88 0.75 1.69 0.76 0.76 2.88 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.84 0.75 1.00 0.7	[0.13; 4.45] 0.7% [0.01; 4.26] 0.2% [0.01; 4.01] 0.2% [0.06; 36.65] 0.2% [0.01; 4.07] 0.2% [0.06; 36.65] 0.2% [0.01; 4.07] 0.2% [0.08; 7.30] 0.4% [0.24; 102.55] 0.2% [0.16; 55.93] 0.3% [0.94; 1.95] 17.0% [0.16; 13.67] 0.5% [0.16; 13.67] 0.5% [0.01; 7.99] 0.2% [0.06; 15.61] 0.3% [0.06; 15.61] 0.3% [0.24; 104.54] 0.2% [0.06; 15.61] 0.3% [0.24; 104.54] 0.2% [0.24; 83.11] 0.3% [0.24; 83.11] 0.3% [0.24; 83.11] 0.3% [0.26; 1.90] 2.0% [0.18; 67.44] 0.3% [0.19; 12.02] 0.5% [0.18; 67.47] 0.3% [0.19; 12.02] 0.5% [0.18; 68.16] 0.3% [0.19; 12.02] 0.5% [0.18; 68.747] 0.3% [0.19; 12.02] 0.5% [0.18; 68.747] 0.3% [0.19; 12.02] 0.5% [0.18; 68.747] 0.3% [0.19; 12.02] 0.5% [0.19; 12.02] 0.5% [0.19; 12.02] 0.5% [0.10; 52.51] 0.2% [0.10; 52.51] 0.2% [0.10; 52.51] 0.2% [0.11; 52.52] 0.2% [0.10; 59.67] 0.2% [0.10; 59.67] 0.2% [0.11; 72.75] 0.2% [0.12; 52.30] 0.2% [0.10; 59.67] 0
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $\rho = 1.00$				0.01	0.1 0.5 2 10	100	

eFigure 17C. Risks of cholecystitis with GLP-1RAs treatments compared with controls by using random-effect models

Study	Experimenta Events Tota	I College	ontrol Total	Risk Ratio	RR	95%-Cl Weight
LEAD-3 Mon(2011) 1860-LIRA-DPP-4 (2011) Astrup et. al. (2012) SCALE Sleep Apnea (2013) SCALE Obesity and Prediabetes (2015) EAGLE study (2015) LEADER (2016) LIRA-RENAL (2016) SCALE Obesity and Prediabetes (2017) PIONEER-4 (2019) SCALE-BT (2020) LIRA-SD2SGLT2! (2020) SUSTAIN-2 (2017) SUSTAIN-2 (2017) SUSTAIN-2 (2017) SUSTAIN-6 (2017) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-8 (2019) SUSTAIN-9 (2019) SUSTAIN-9 (2019) PIONEER-3 (2019) PIONEER-1 (2019) PIONEER-1 (2019) PIONEER-2 (2019) PIONEER-3 (2019) PIONEER-6 (2019) PIONEER-6 (2019) PIONEER-6 (2019) AWARD-7 (2018) AWARD-7 (2018) AWARD-7 (2018) AWARD-10-10 (2018) REWIND (2019) DURATION-2 (2010) EUREXA (2012) Diamant et. al. (2014) DURATION-3 (2014) EXCEL (2017) DURATION-8 (2020) GETGOAL-Pu (2013) GETGOAL-Pu (2013) GETGOAL-P (2013) GETGOAL-S (2014) HARMONEY-1 (2014) HARMONEY-1 (2014) HARMONEY-4 (2014) HARMONEY-6 (2018) Rosenstock et. al. (2020)	1 63 1 48 36 468 1 14	1 0 1 1 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	248 219 95 179 487 212 484 4672 137 747 140 100 401 360 1649 133 135 399 204 80 71 171 171 171 171 171 171 171	0.1 0.5 2 10	0.50 - 2.548 - 1.48 4.43 1.71 0.69 0.20 0.33 1.22 - 1.52 0.33 - 1.50 0.53 - 1.54 0.50 - 4.70 0.07 - 2.96 1.27 0.34	[0.06; 36.65] 0.3% [0.01; 4.07] 0.3% [0.06; 36.55] 0.4% [0.01; 8.27] 0.3% [0.37; 25.29] 0.8% [0.12; 73.92] 0.3% [1.02; 71.45] 0.3% [0.12; 71.45] 0.3% [0.12; 71.45] 0.3% [0.06; 36.65] 0.3% [0.18; 21.50] 0.6% [0.06; 36.65] 0.3% [0.16; 63.22] 0.3% [0.17; 1.66] 2.3% [0.06; 36.65] 0.3% [0.16; 63.2] 0.4% [0.06; 36.44] 0.3% [0.01; 8.20] 0.3% [0.16; 51.66] 2.3% [0.16; 51.66] 2.3% [0.16; 67.94] 0.4% [0.03; 48.7] 0.3% [0.16; 55.54] 0.4% [0.06; 36.44] 0.3% [0.16; 55.54] 0.4% [0.06; 36.85] 0.4% [0.06; 36.85] 0.3% [0.16; 55.54] 0.4% [0.03; 14.87] 0.3% [0.18; 21.92] 0.6% [0.16; 55.54] 0.4% [0.03; 7.92] 0.4% [0.03; 7.92] 0.4% [0.03; 7.92] 0.4% [0.04; 24.90] 0.3% [0.18; 21.92] 0.6% [0.18; 21.92] 0.6% [0.18; 21.92] 0.6% [0.18; 21.92] 0.6% [0.18; 21.92] 0.4% [0.03; 7.92] 0.4% [0.03; 7.92] 0.4% [0.06; 36.28] 0.3% [0.24; 81.89] 0.4% [0.07; 3.56] 0.9% [0.12; 52.70] 0.4% [0.06; 36.28] 0.3% [0.22; 3.30] 0.4% [0.01; 8.18] 0.3% [0.00; 1.66] 35.5% [0.00; 36.48] 0.3% [0.01; 8.14] 0.3% [0.00; 1.66] 35.5% [0.00; 36.48] 0.3% [0.01; 8.14] 0.3% [0.02; 2.74] 0.6% [0.06; 36.48] 0.3% [0.07; 3.09] 6.9% [0.05; 5.49] 6.9% [0.05; 5.49] 6.9% [0.05; 5.49] 6.9% [0.12; 72.30] 0.4% [0.01; 8.42] 0.3% [0.12; 2.730] 0.4% [0.01; 8.42] 0.3% [0.12; 2.730] 0.4% [0.01; 8.42] 0.3% [0.12; 2.730] 0.4% [0.05; 5.49] 6.9% [0.05; 5.49] 6.9% [0.05; 5.49] 6.9% [0.12; 72.30] 0.3% [0.12; 2.730] 0.3% [0.12; 2.730] 0.3% [0.12; 2.730] 0.4% [0.05; 5.49] 6.9%
			0.01	0.1 0.0 2 10	100	

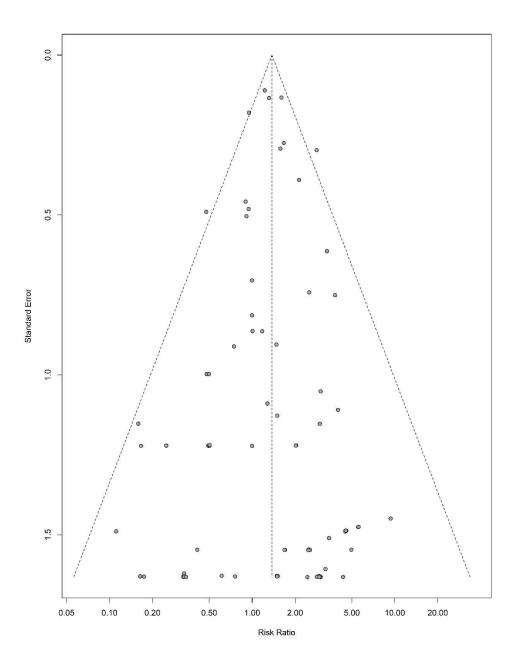
eFigure 17D. Risks of biliary diseases with GLP-1RAs treatments by using random-effect models

Study	Experin Events		C Events	ontrol Total	Risk	Ratio	RR	95%-CI	Weight
1860-LIRA-DPP-4 (2011) SCALE Obesity and Prediabetes (2015) SCALE Diabetes (2015) LEADER (2016) SCALE Obesity and Prediabetes (2017) SUSTAIN-6 (2017) SUSTAIN China (2021) STEP-3 (2021) Newsome et. al. (2021) PIONEER-3 (2019) PIONEER-2 (2019) PIONEER-6 (2019) PIONEER-6 (2019) AWARD-CHN1 (2018) REWIND (2019) Inagaki et. al. 2012 DURATION-3 (2014) EXCEL (2017) DURATION-8 (2020) ELIXA (2015) HARMONEY-3 (2014) Harmony outcome (2018) Random effects model	2 25 5 5 1 1 3 1 0 2 2 1 1 0 2 1 1 0 2 1	439 957 6698 1501 1648 577 407 239 1395 4943 7347 492 4943 7347 302 4717 36225	0 0 0 0 16 0 0 0 0 0 0 1 1 1 0 1 2 0 0 2 1 1 1	219 ← 4678 747 1649 ← 290 ← 290 ← 409 ← 1592 ← 243 ← 4949 ← 212 ← 223 ← 7390 ← 710 ← 4716 32741 ← 32741 ← 4716	- -	*	→ 1.53 → 1.68 → 1.54 → 1.54 → 1.51 → 1.51 → 1.51 → 1.00 → 0.33 → 2.00 → 1.48 - 1.67 → 2.95 → 0.03 → 1.01 → 1.52 → 0.78 → 4.00	[0.12; 51.79] [0.06; 37.42] [0.08; 34.85] [0.83; 2.91] [0.30; 98.90] [0.34; 4.65] [0.06; 36.79] [0.12; 45.06] [0.04; 24.58] [0.01; 8.14] [0.18; 22.05] [0.06; 36.28] [0.06; 36.28] [0.06; 36.28] [0.06; 37.12] [0.07; 8.14] [0.07; 72.21] [0.07; 8.14] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12] [0.08; 37.12]	1.5% 1.3% 34.8% 1.6% 7.9% 1.3% 1.3% 1.3% 26.7% 1.3% 26.7% 1.3% 24.4% 1.3% 2.8%
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 1.00$				0.2	0.5	1 2	5		

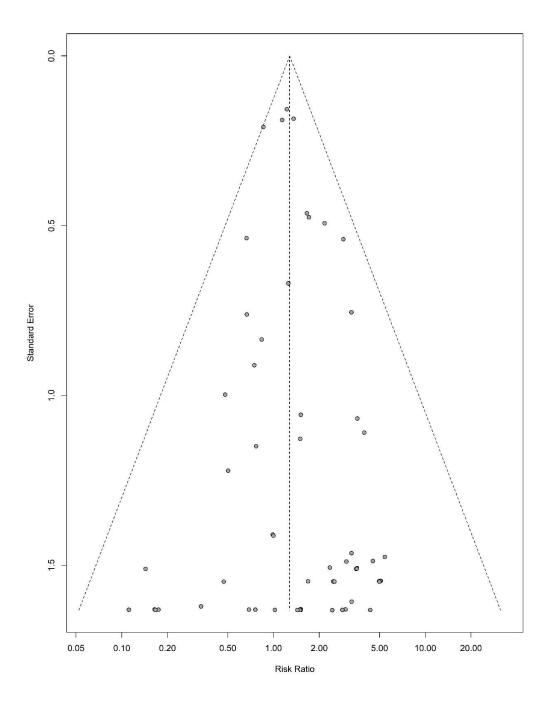
eFigure 18. Funnel plots

Notes: Experimental, GLP-1RAs treatments; Control, placebo or active control. **Abbreviations:** GLP-1RAs, glucagon-like peptide 1 receptor agonists; RR, relative risk; CI, confidence interval.

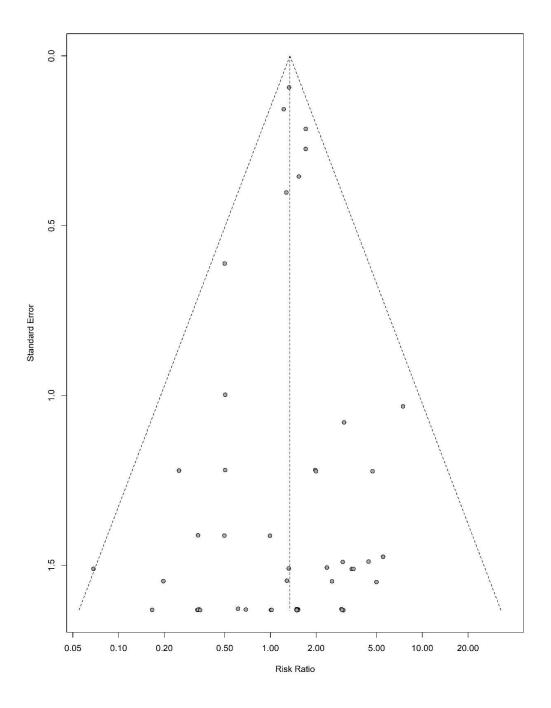
eFigure 19A. Funnel plot of studies included for the association between GLP-1RAs and the risks of gallbladder or biliary diseases



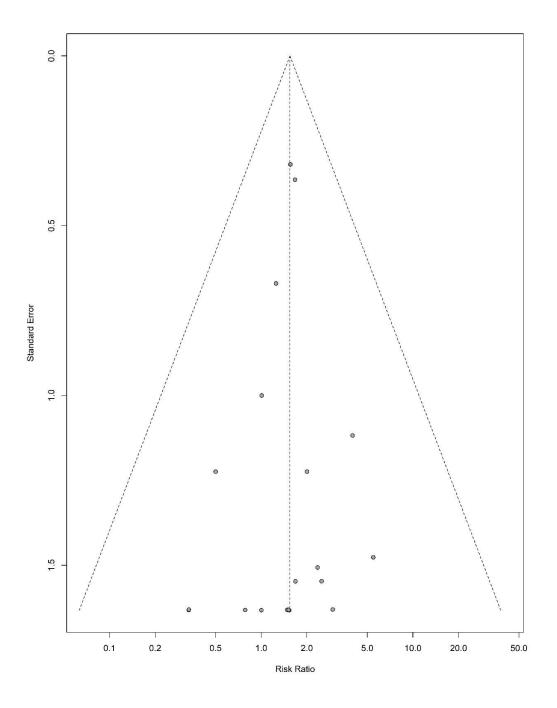
eFigure 18B. Funnel plot of studies included for the association between GLP-1RAs and the risks of cholelithiasis



eFigure 18C. Funnel plot of studies included for the association between GLP-1RAs and the risks of cholecystitis



eFigure 18D. Funnel plot of studies included for the association between GLP-1RAs and the risks of biliary diseases



eResults. Risks of gallbladder or biliary diseases in patients with GLP-1RAs treatments compared with controls in all trials

Abbreviations: RR, relative risk; CI, confidence intervals. Experimental, GLP-1RA treatments;

Control, placebo or active control.

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